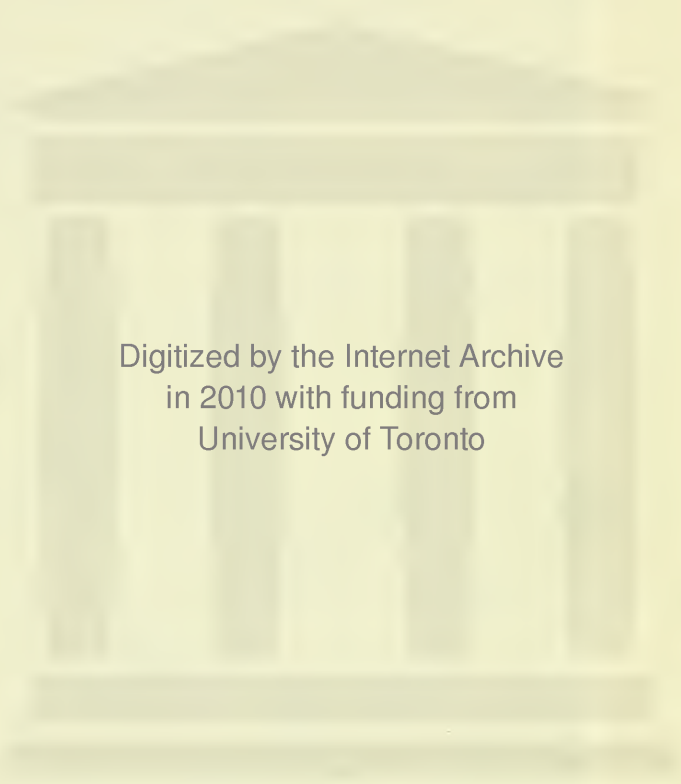




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TREASURY DEPARTMENT

Public Health and Marine-Hospital Service of the United States

PUBLIC HEALTH BULLETIN No. 47 -50

SEPTEMBER, 1911

1911-1912

STUDIES UPON LEPROSY

XIV. THE ARTIFICIAL CULTIVATION OF THE BACILLUS
OF LEPROSY

XV. ATTEMPTS AT SPECIFIC THERAPY IN LEPROSY

BY

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Investigations made in accordance with
the Act of Congress approved
March 3, 1905



WASHINGTON
GOVERNMENT PRINTING OFFICE

1912

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no. 47-50

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CULTIVATION OF THE BACILLUS OF LEPROSY.

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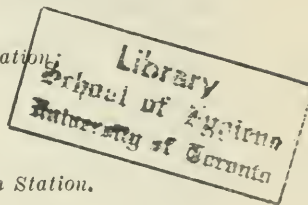
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INTRODUCTION.

The greatest obstacle that has been met with in the past investigations of leprosy has been our inability to artificially propagate the bacillus, either on culture media or in laboratory animals.

Without this knowledge studies in specific therapy were at least difficult, if not quite impossible; and studies in transmission were limited chiefly to clinical observations, or to the mere recording of the findings of lepra bacilli in certain tissues or discharges of lepers, or insects or objects that had come into contact with lepers. If the results which we record here are confirmed by others and become generally accepted, there should result a renewed interest in this disease in both leprous and nonleprous countries, and such interest may possibly result in the acquisition of knowledge that will be of use in the control of this disease.

REVIEW OF LITERATURE.

Bacterial rods were first described as being present in a leproma by Hansen (1) in 1868 and 1873, and by Vandeycke Carter (1); these observations were soon afterwards confirmed by Klebs (1), Auspitz (1), Daniellsen (1), and Neisser (1). From that time up to the present numerous attempts have been made, as the below-given literature will indicate, to cultivate this organism on artificial media; but up to 1909, when Clegg (52) was successful in repeatedly growing acid-fast bacilli, morphologically identical with the organism found in

leproma, in symbiosis with cholera and amœba, it is doubtful whether any success had been met with in the artificial cultivation of this organism, and certainly no one has been able to carry cultures on for several generations.

The following brief review of the literature on this subject is, however, of interest as showing the difficulties met with in the attempts to cultivate this organism and by showing the futility of attempting to grow this bacillus on ordinary media, and thus prepared the way for its final successful cultivation.

Neisser (2), 1886, attempted to cultivate the bacillus on gelatin-blood serum and cooked egg. He thought that slow multiplication occurred on these media, but his experiments were not productive of any practical results.

Bordoni-Uffreduzzi (3), 1887, first reviews the work of previous investigators in their attempts to cultivate the bacillus of leprosy, quoting Fraenkel as stating that heretofore no success had been met with in growing this bacillus on artificial media, and also stating that Fluegge (*Die Mikroorganismen*, usw., 1886, 2. Aufl., p. 221), Hansen (*Virchow's Archive*, 1882, vol. 90, p. 542), Neisser (2), and Crookshank (*Manual pratique de bacteriologie*, Trad. par Bergeaud, Brussels, 1886) had been entirely unsuccessful in their attempts at growing this organism outside of the body.

Bordoni-Uffreduzzi then goes on to describe his own cultural attempts. He uses as media bouillon, gelatin, agar-agar, and coagulated blood serum, as well as spinal marrow, on peptone-glycerin serum; on the latter media he secured a growth of what he thought was the lepra bacillus.

The same author (4), 1887, describes the organism which he grew from leprous material on spinal marrow media, and his description seems to indicate that the bacterium is one of the nonacid-fast diphtheroid group.

The same author (5), 1888, replies to certain criticisms of Baumgarten regarding his organism, and attempts to uphold his claim of having cultivated the bacillus of leprosy.

Baumgarten (7), 1888, sums up, in a manner unfavorable to the claims of Bordoni-Uffreduzzi, the controversy over the bacillus grown by that investigator.

Beavan Rake (8), 1888, employed the serum of lepers either as a fluid or solidified with agar or gelatin. On these media he grew a number of organisms, but none of them were acid fast.

Gianturco (9), 1889, employed glycerin agar and cultivated what appeared to be a similar organism to that isolated by Bordoni-Uffreduzzi, and he believes his bacillus to be identical with Bordoni-Uffreduzzi's organism.

Bordoni-Uffreduzzi (10), 1889, agrees with Gianturco that they have isolated identical organisms.

Campana (11), 1889, describes 500 attempts which he made to grow the bacillus of leprosy on artificial media, all of which, however, resulted in failure, and from this experience he doubts the claim made by other investigators that this bacillus could be grown on certain artificial media.

Beavan Rake's (12), 1891, work is reviewed in an editorial of the *Lancet*, 1891, and the statement made that all of this investigator's attempts have proven negative.

Holst (13), 1891, believed that failure to cultivate the bacillus of leprosy was due to the organisms in old lepromata being dead. He therefore chose only new nodules in his work, thus hoping to secure live bacilli; his attempts at artificial cultivation were, however, entirely negative.

Campana (14), 1891, isolated an anaerobic, nonacid-fast bacillus from a leproma and believed this organism to be the bacillus of leprosy.

Kanthack and Barclay (15), 1891, employed bouillon and glycerin agar for media and were successful in growing an acid-fast organism from a leproma. This peculiarity of acid fastness appeared to be variable, however, as after growing for some time on artificial media it became almost nonacid fast, and still later regained its acid fastness. These investigators were at first inclined to consider this organism to be *B. lepræ*, but in a subsequent communication they withdrew this claim.

Campana (16), 1891, describes further culture peculiarities of the bacillus which he isolated.

Ducrey (17), 1892, isolated a bacillus, probably identical to Campana's bacillus, from a leproma, and found that, like Campana's organism, it was very little, if at all, acid fast.

At the "Lepra Discussion" (18), 1892, the organism isolated by Campana was discussed.

Campana (19), 1892, again discusses the method he employed in the cultivation of an anaerobic nonacid-fast bacillus from a leproma.

Wolters (20), 1893, reviews some of the cultural attempts made to date and judges all previously reported successes to be either doubtful or negative. He himself thinks that he once secured, while working in Doutrelepon's clinic, a single *B. lepræ* colony on glycerin agar.

A commission composed of Beavan Rake, Buckmaster, and Thompson (21), 1893, report attempting to grow *B. lepræ* on various media, but that they only succeeded in growing a liquefying, non-acid-fast bacillus.

Campana (22), 1894, describes the morphology of the bacillus which he isolated (previously referred to). The media he employed was agar, mixed with bouillon, peptone, and glucose. The organism grows anaerobically and is neither alcohol nor acid fast.

Levy (24), 1898, succeeded in growing an organism on glycerin agar from the blood of a leper. This organism is nonacid fast, or very slightly acid fast. With this rather important exception, it resembled "the bacillus of bovine tuberculosis," or possibly a streptothrix.

The same author (25), 1898, again refers to the organism which he grew from a leper. He considers that it is a streptothrix and probably identical to Czaplewski's organism. He considers this organism of only academic interest, and not *B. lepræ*.

Czaplewski (26), 1898, grew from the nasal secretion of a leper an organism which he believes belongs to the "Sklerothrixgruppe." This organism retains its acid fastness in cultures. He denies the claim of Levy that this organism is identical with Levy's and therefore a streptothrix.

Spronck (28), 1898, succeeded in growing a bacillus from a leproma, using glycerin-potato as media. This organism, from his description, appears to be a member of the pseudo-diphtheria group.

Levy (29), 1899, again writes on the organism which he isolated from a leper, and still believes it to be a streptothrix. He mentions Babes, Spronck, and Czaplewski as having grown the same organism as himself, while, on the other hand, Bordoni-Uffreduzzi's, Gianturco's, and Campana's publications deal, in his opinion, with a different organism.

Teich (31), 1899, claims to have grown an acid-fast, pleomorphic organism from five cases of leprosy. He used potato agar as a media.

Bordoni-Uffreduzzi (32), 1899, reviews what he considers his successful attempt to grow the bacillus of leprosy, and states that Gianturco, Spronck, Czaplewski, and Barannikow all later grew the same organism, and all regarded it as an acid-fast bacillus.

Babes (33), 1899, refers to a previous article (*Zeitschrift fuer Hygiene*, 1889, February, p. 173) and to Czaplewski's description (*Centralblatt für Bakteriologie*, etc., *Originale*, No. 13, 1898), also to the work of Cornil and Babes in 1890. In his present article Babes gives a full description of an organism which he previously isolated, and which he believes belongs to the pseudo-diphtheria group. In his cultures he occasionally observed branching forms. He has succeeded in isolating this organism from the nodules of 12 lepers.

Barannikow (34), 1899, grew a bacillus from a leproma, which resembles the organism of Babes, Bordoni-Uffreduzzi, and others; that is to say is a member of the pseudo-diphtheria group.

Carrasquilla (34a), 1899, grew what he believed to be lepra bacilli on coagulated human serum. The organism was motile and aerobic.

Kedrowski (35), 1900, used placenta for media, and succeeded in growing four different varieties of streptothrix, all of which were more or less completely acid-fast.

Scholtz and Klingmüller (36), 1900, reported complete failure to grow the bacillus of leprosy, and express the opinion that no one else had succeeded up to that time.

Pushtiwoi (37), 1902, used potato as media, and by this means succeeded in isolating a bacillus from a leper. No description of this bacterium is given in the abstract of this article in "Lepra Bibliotheca Internationalis," and his original article is inaccessible to us.

Van Houtum (38 and 38a), 1902, attempted to cultivate the bacillus of leprosy on various media, and states that he found that by starting his cultures on fish bouillon, containing a small portion of beef bouillon, the organism multiplied. From the abstract (Lepra Bibliotheca Internationalis, vol. 5; the original article is inaccessible to us) it appears that he then transferred this bouillon culture to glycerin-glucose-agar slants, on which latter media the organism he was dealing with grew well. The bacillus he isolated was nonacid-fast and liquefied gelatin.

Kedrowski (39), 1902, has grown a number of branching forms of either streptothrix or other higher forms from leprosy nodules. He employed as a media an extract of placenta which, after sterilization by filtration, was added to agar.

Barannikow (40), 1902, grew a nonacid-fast bacterium from a leproma and believed it to be *B. lepræ*.

Zenoni (41), 1902, claims to have cultivated a nonacid-fast bacillus from the skin lesions of a leper. This bacterium caused the death of white mice in from 2 to 13 days.

Levy (42), 1902, claims that after growing on garden beets for one generation his organism will grow on glycerin bouillon, and on this latter media it resembles the bacillus of diphtheria.

Gjubert (43), 1903, employed, as media, calf's brain emulsion in agar, and reports what he believed to be a successful attempt to cultivate *B. lepræ*.

Zenoni (45), 1904, states that the "best" artificial media for the cultivation of the lepra bacillus is the serum of lepers, inactivated at 55° C. By employing this media he succeeded in growing a nonacid-fast organism, apparently belonging to the pseudo-diphtheria group. He inoculated white rats with this organism and caused lesions which, in his opinion, resemble human lepromata.

Rost (46), 1904, prepared numerous salt-free media, and on these believes he succeeded in growing *B. lepræ*.

Rost (47), 1905, reiterates his claim that lepra bacilli will grow on salt-free media, the growth appearing in bouillon, freed from sodium chloride, from three to five days after inoculation with leprous material. He uses his cultures to obtain an extract for therapeutic purposes.

Editorial, *Lancet* (48), 1905, refers to Semple's work disproving Rost's claim to have grown the bacillus of leprosy.

Weil (49), 1906, employed several media, among which were glycerin-glucose agar, containing noncoagulated, human pleuritic serum; glucose peptone agar, containing noncoagulated, human pleuritic serum; live hen's egg, etc. On several of these media, but especially on the hen's egg, this investigator thought he was successful in securing a growth of the bacillus of leprosy for one generation. The growth was stated to begin on the fifth day, proceed up to the twenty-fifth day, after which no further development occurred. The colonies produced were of a light-yellowish color. Weil did not succeed in transferring these colonies beyond the first generation.

Campana (51), 1909, describes again the bacillus which he grew from a leper, under anaerobic conditions, on glucose media.

Clegg (52), 1909, grew amœba and *S. cholerae* in symbiosis on plain agar and weakly nutrient agar. The amœba which he employed were obtained from several sources (animals' intestinal tracts and pond water). To these two symbionts, when growing well together, leprous material was added. A few days after this addition morphological changes were seen to occur in the lepra bacilli, the long slim rods noted in tissues became beaded, and from the deeply stained portions of these beaded bacilli short, plump rods developed. By further multiplication chains longer than the original clumps, composed of many short bacilli, were noted in the culture media. After this morphological change had occurred, multiplication continued. At the end of a week or 10 days transfers were made to plain agar tubes, and this process of transfer continued until he secured multiplying subcultures 10 or more generations removed from the original inoculation. These later generation tubes contained many more acid-fast bacilli than the original tube, showing that multiplication had occurred. At the time this first paper was written Clegg had not isolated the acid-fast organism in pure culture.

Clegg (53), 1909, since writing the last article, continued his experiments on the artificial cultivation of the leprosy bacillus in symbiosis with *S. cholerae* and amœba, and at the time of writing this article had succeeded in growing acid-fast bacilli seven times from as many cases of leprosy. All of these seven cultures were grown in symbiosis with amœba and cholera. The cultures were secured from as unlike sources as the skin nodules of a living leper and the splenic pulp of a dead leper.

At the time of publishing this paper he had succeeded in two instances (cultures from two cases of leprosy) in isolating this acid-fast organism in pure culture. He gives a full description of the cultural peculiarities of this acid-fast rod, as well as its morphology, and a description of several probably unsuccessful attempts to produce leprosy in laboratory animals.

He closes this article with the following summary:

1. The leprosy bacillus was first cultivated from leprosy material in symbiosis with other unidentified bacteria and amœba, and later from other cases in symbiosis with amœba and the cholera vibron.

2. By heating a symbiotic culture of amœba, cholera, and leprosy for half an hour at 60° C. and incubating, the leprosy bacillus was obtained in pure culture.

3. The leprosy bacillus, isolated in this manner, grows readily on the ordinary laboratory culture media.

4. The bacillus is pathogenic for guinea pigs, subcutaneous inoculations having caused lesions, which macroscopically and microscopically resemble the leprosy lesions of the human subjects.

Currie, Brinckerhoff, and Hollmann (54), 1910, working in Hawaii, undertook to either confirm or disprove the work that Clegg had done in the Philippine Islands.

After several failures in the preliminary attempts, these three investigators finally succeeded in growing acid-fast bacilli four times (from three cases of leprosy) in symbiosis with *S. cholerae* and amœba. Of the two symbionts employed the cholera spirillum was obtained from the Hygienic Laboratory in Washington, and the amœba were isolated from guinea pigs' intestines in Hawaii, so it can be seen that there was no connection between symbionts used by Clegg and those used by Currie, Brinckerhoff, and Hollmann, and therefore there existed no common source of possible error.

Currie, Brinckerhoff, and Hollmann (54), after growing these four "strains" of acid-fast bacilli in symbiosis for a number of generations, had succeeded, at the time that this article was published, in isolating one "strain" of acid-fast bacilli in pure culture,¹ and this pure culture was identical in its several peculiarities to the bacilli described by Clegg in Manila.

Duval (55), 1910, working in New Orleans, La., with entirely different "strains" of *S. cholerae* and amœba, as well as with different patients, succeeded in cultivating, by the method of Clegg, acid-fast bacilli from leprosy nodules and isolated some of these bacilli in pure culture.

Twort (56), 1910, employed Dorsett's egg media, which he inoculated with leprosy material. To this material he added killed ground-

¹ It may be stated here that the organism just mentioned that was isolated in pure culture by these investigators was designated "B" and will be referred to later in this bulletin under that designation.

up tubercle bacilli, and after considerable time secured a thin, colorless growth, which he believes to be a culture of *B. lepræ*.

Duval and Gurd (57), 1911, refer to Duval's work in confirming the investigations of Clegg. They then state that while amœba and *S. cholerae symbiosis*, plus leprous material, results in the growth of lepra bacilli, the same result can also be obtained by transplanting leprous material (without either the addition of cholera or amœba) into a media containing tryptophan, cystein, etc., and they claim to have grown acid-fast bacilli by this means from the nasal discharges of lepers. They then describe the morphological differences between new and old cultures of their bacilli.

Duval (58), 1911, again describes the cultivation of the bacillus of leprosy by the method of Clegg, and speaks further on his claim that amœba and *S. cholerae* can be dispensed with, and the organism of leprosy grown by adding amino acids to the culture media.

Williams (59), 1911, used ordinary broth and also Rost's media, and succeeded in growing five apparently different organisms from as many cases of leprosy. One of these was an acid-fast bacillus, one a nonacid-fast streptothrix, another an acid-fast streptothrix, and still another a nonacid-fast diphtheroid, etc.

This investigator considers that his work tends to confirm the work of Rost, Deycke, and Clegg, i. e., that all of these investigators have, by different methods, isolated the same organism, which latter is very pleomorphic. He seems, however, to base this opinion on very little data other than that the organisms in question were all grown from lepromata and that local nodules were produced in animals by the inoculation of some of these cultures.

TECHNIQUE.

The authors of this article have nothing to add to the technique to be employed in the artificial cultivation of the bacillus of leprosy, beyond that described first by Clegg (52) and repeated by Currie, Brinckerhoff, and Hollmann (54), except possibly to emphasize the great importance of having absolutely pure *S. cholerae* and amœba cultures before the leprous tissue is added; as well as the employment of control experiments to show that no acid-fast or nonacid-fast rod exists in the leprous tissue (that is capable of growing on ordinary media) before the two symbiotic organisms have been added to it. Accidental contamination of symbiants or leprous tissue with saprophytic, acid-fast organisms would probably not often occur: nevertheless such a possibility exists, and therefore the precautions indicated should be invariably taken by investigators carrying on this line of work.

We might mention also, in way of encouragement to others, that after every condition that we are familiar with has been complied

with it is still the exception to obtain a culture of *B. lepræ*; but of many tubes inoculated only a small percentage show multiplication of the acid-fast organisms, and even of this small percentage many cultures die out before they reach the third generation. The reason for this fact can not be given, but it is hardly strange that such should occur, when we know that similar failures often result in attempts to cultivate the bacillus of tuberculosis, even when conditions appear to favor such cultivation.

**PRESENT STATUS OF THE ARTIFICIAL CULTIVATION AND STUDY OF
B. LEPRÆ AT THE UNITED STATES LEPROSY-INVESTIGATION
STATION, HAWAII.**

Up to the present time the authors of this bulletin (including the independent work of Clegg in Manila, the independent work of Currie, Brinckerhoff, and Hollmann in Hawaii, and the joint work of Currie, Clegg, and Hollmann in Hawaii) have succeeded in growing acid-fast bacilli in symbiosis with cholera and amœba at least 16 times from 15 cases of leprosy, and have succeeded in isolating such acid-fast bacilli in pure culture 7 times.

The following is the designation and source of the seven "strains" of pure culture of acid-fast bacilli that we are now carrying on at the laboratory in Honolulu:

"F," grown and isolated in pure culture by Clegg in Manila and described in his previous article. (53.)

"G," grown and isolated in pure culture by Clegg in Manila and described in his previous article. (53.)

"B," grown and isolated in pure culture by Currie, Brinckerhoff, and Hollmann in Hawaii and mentioned in their previous article (54) as having been isolated in pure culture.

"A," grown and isolated in pure culture by Currie, Brinckerhoff, and Hollmann in Hawaii and mentioned in their previous article (54) as at that time still growing in symbiosis with the *S. cholerae* and amœba.

"E," grown and isolated in pure culture by Currie, Brinckerhoff, and Hollmann in Hawaii.

"H," grown by Currie, Brinckerhoff, and Hollmann and mentioned in their previous article (54) as at that time still growing in symbiosis with the *S. cholerae* and amœba, and later isolated in pure culture by Currie, Clegg, and Hollmann, working jointly in Hawaii.

"18," grown and isolated in pure culture by Currie, Clegg, and Hollmann, working jointly in Hawaii.

Of the above organisms, "18" has been isolated too recently for us to be able to describe fully its cultural peculiarities, but so far appears to be identical with other "strains."

The following is a description of our several organisms, and for comparative purposes we have also described the well-known *B.*

margarin, *B. smegmæ* and Moellers grass bacillus (all of them obtained from Harvard Medical School).

DESCRIPTION OF THE CULTURAL PECULIARITIES OF OUR ORGANISMS OTHER THAN "18."

The following is a description of the *B. lepræ* "strains" (except "18"). These organisms resemble each other so closely that it is impossible to tell one culture tube from the other, and we have therefore, for the sake of brevity, made one description apply to all.

Culture on ordinary bouillon.—In young cultures a fine flocculent growth, adhering to the sides of the tube, from which attachments it sends out stalactites. No clouding of the fluid; no pellicle formation. On shaking the tube, a thick, tenacious sediment arises from the bottom. In very young cultures the appearance in bouillon is quite similar to a *B. pestis* or *Streptococcus* culture. Old cultures differ from the above description in having a heavy wrinkled surface growth, which in time becomes of a golden yellow color.

Glycerin bouillon.—The same as ordinary bouillon, except that the organism grows more rapidly and more luxuriantly in this media than in the last named.

Glycerin agar.—Growth on this media varies in color from a canary yellow to a deep orange, the latter shades being more commonly met with, but slight shades of color variations, independent of any apparent cause, are commonly noted.

The growth extends slightly beyond the track of the needle stroke, and varies from a slimy to a granular appearance. Surface may be smooth and shining, or rough and nodular, but never truly wrinkled, as is noted in some of this group. Edges of the culture are raised, smooth, sharply defined. Growth is always moist, but this varies somewhat with reaction of the media. On media just neutral, cultures are apt to be drier and more granular, while on fully alkaline media the growth is more moist, even to the point of being slimy.

Plain agar.—Growth much thinner on this media than on that containing glycerin and other nutrient media. Spreads little beyond the track of the needle stroke (this depends, however, somewhat on the moisture of the media). Except that it is less luxuriant, the culture is of the same appearance as that noted on glycerin agar.

Ordinary nutrient agar.—Growth heavier than on plain agar, but not as heavy as on glycerin agar, of light yellow to reddish yellow (orange) color, confined to the track of the needle stroke. Surface usually smooth, but sometimes nodular from the heaping up of colonies.

Dorsett's egg media.—Growth invariably of a deep orange shade of yellow, none of these "strains" showing the lighter shades of yellow

on this media. Growth is confined to the path of the needle stroke, or spreads very little beyond it; very dry, "mealy," granular in appearance, showing neither wrinkling nor glistening of surface. Borders clearly defined, slightly raised above the level of the media. No liquifaction of media at the end of a month's growth.

Potato (neutral in reaction).—Growth confined to the path of the needle stroke, of a deep orange-yellow color, dry, "mealy" in character, surface rough from the coalescence of numerous small colonies, but without any tendency to show wrinkling.

Dunham's peptone.—Fluid clear and devoid of growth of any character, except at the bottom, where a yellowish sediment occurs, which sends up flocculent threads which float in media. At the time these notes were taken, no pellicle¹ had formed on the media.

Glucose broth (in fermentation tubes).—A heavy, slightly wrinkled yellow pellicle covers the surface of the fluid and adheres to the sides of the glass in the aerobic portion of the tube. No growth in the anaerobic portion of the tube. No gas is produced.

Lactose, mannite, and saccharose broth in fermentation tubes.—Identical in appearance to glucose-broth culture.

Blood serum (Loeffler's).—Organism spreads considerably beyond track of the needle stroke, probably due to the moisture of the media; color of a light orange yellow, shading into canary yellow at the edges of the culture. Surface moist, smooth, glistening; growth slimy and tenacious. In our experience at this station blood serum is not liquefied by this organism, even at the end of a month's growth.

Nutrient gelatin (stab culture).—A heaped-up growth occurs on surface surrounding point of inoculation, very slight growth along the path of the needle stab, lightness of growth in depths of media as compared to surface, apparently being due to the air-loving propensities of the bacillus, as growth becomes progressively lighter as it proceeds down the needle stroke. No liquefaction of the media occurs.

Serum tests.—Medium-sized horse immunized for three months with repeated injections of live cultures of "strains" "B," "F," "G," and "H." After several weeks serum of this animal was collected in the usual manner and employed in various dilutions with the following results:

In any dilution below 1:1000 marked clumping occurs with all the acid-fast organisms that we have isolated.

In any dilution below 1:500 very strong clumping of the above-mentioned organisms occurs.

¹ This is a question of age and chance. If the loopful of bacilli used to inoculate the media sinks to the bottom, in time stalactites come up from the bottom and eventually reach the surface, and from these pellicles are formed; if, on the other hand, care is employed (or better, a drop of sterile oil is used to float the inoculation) to float the loopful of bacilli used to inoculate the tube, a pellicle forms in a few days on the surface of the fluid. This is true in all fluid media employed.

The serum of this horse is not in the least bacteriolytic, or even capable of altering the morphology, in any strength solution, of our organisms.

In the few experiments made this serum, in a dilution of 1:40 prevented the bacilli "B," "F," "G," and "H" from growing after exposure for a short time, while cholera spirilla grew readily when mixed with these organisms as controls and after being subjected to the same action of the serum. This test must be repeated, but our data up to the present appear to indicate that the serum in question, in 1 to 40 dilution, is bacteriocidal for these four "strains" of *B. lepræ*.

DESCRIPTION OF OTHER ACID-FAST ORGANISMS.

(For purpose of comparison to the lepra cultures just described.)

1. GRASS BACILLUS OF MOELLER.

Ordinary broth.—A thin pellicle of lightish yellow color covers the surface of the fluid and adheres to the glass. There is a fine flocculent precipitate at bottom of the tube, adhering to the sides of the tube. The fluid is perfectly clear.

Glucose broth.—Same as ordinary broth, except that the growth is somewhat heavier.

Glycerin broth.—Growth spreads far beyond the path of the needle stroke, in fact almost to the border of the media. Almost white in color, with a slight yellow tint; surface smooth, glistening, moderately moist, border sharply defined but irregular in contour.

Plain agar.—Growth extends beyond the track of the needle stroke, of light yellow color, thin, transparent, with sharply defined irregular borders, surface smooth, moist, and glistening.

Nutrient agar.—Growth extends beyond the track of the needle stroke, to the limits of the media; white in color or of a slight yellow tinge; borders sharply defined but irregular in outline. Surface granular in appearance, moderately moist, without any tendency to wrinkle.

Dorsett's egg media.—Growth spreads far beyond the path of the needle stroke and is of a deep orange color; borders slightly raised, sharply defined, but irregular in outline. Surface dry and without luster.

Potato (neutral in reaction).—Growth spreads to limit of media, very slightly raised above the surface of the media, of a drab-gray color; dry, granular, and "mealy" in appearance, shows no tendency to wrinkle.

¹ Moeller has isolated several "strains" of grass bacilli. In passing through many hands the identification of this one has been lost. Our culture was procured from Harvard Medical School.

Dunham's peptone.—Media perfectly clear, the only growth present being a slight amount of flocculent precipitate at the bottom of the tube.

Glucose broth in fermentation tube.—Heavy white pellicle adherent to glass. The organism, unlike *B. lepræ*, grows for a short distance into the anaerobic portion of the tube; no gas has been formed.

Lactose, mannite, and saccharose broth in fermentation tubes.—Growth identical in appearance to that in glucose broth.

Blood serum.—Growth extends considerably beyond the path of the needle stroke, is of a light yellow color, with sharp, well defined but irregularly shaped borders. The growth is moist, surface glistening, and shows no wrinkling. No liquefaction of the media occurs.

II. BACILLUS MARGARIN.

Ordinary broth.—A heavy, yellowish sediment at the bottom of tube, with a fine flocculent precipitate adherent to sides of tube. The media remains clear. (This organism, when the culture is several weeks old, often shows a pellicle. The cultures we are describing, like in case of *B. lepræ*, are too young to show a pellicle formation).

Glycerin broth.—Same as ordinary broth, except that the growth is heavier.

Potato (neutral in reaction).—Growth rather scant, confined to the track of the needle stroke, very slightly raised above the level of the surrounding media, of a light, golden-yellow color, moist, glistening and smooth surface, without any tendency to wrinkle.

Dunham's peptone.—White flocculent precipitate at the bottom of tube; fine flocculi adhere to sides of tube, media clear, no pellicle formation.

Glucose broth in fermentation tube.—Flocculent cloud occupying the whole aerobic portion and extending a very slight way into the anaerobic portion of tube. No gas formation is shown.

Lactose, mannite, and saccharose broth in fermentation tubes.—Identical in appearance to glucose-broth cultures.

Blood serum (coagulated).—Growth spreading a considerable distance beyond the path of the needle stroke, of a light yellowish color, with sharply defined but irregular borders. Surface moist, glistening, and smooth. No liquifaction of media.

Glycerin agar.—Growth confined to the path of the needle stroke, of light canary-yellow color, with clearly defined but irregular borders. Surface smooth, glistening, moist: in places surface shows slight tendency to wrinkle. With the exception of this last peculiarity, this agar culture could not be told from the cultures of *B. lepræ*, which we have.

Plain agar.—Shows a thin, semitransparent, light-yellowish growth, having well-defined borders and a smooth, glistening surface.

Ordinary nutrient agar.—Growth of light-yellow color which spreads somewhat beyond the path of the needle stroke. Growth shows well defined, irregularly shaped borders, slightly raised above the general level of the media. Surface smooth, glistening, and moist in appearance.

Dorsett's egg media.—Growth spreads considerably beyond the path of the needle stroke, smooth in places, slightly granular in others, depending on the amount of moisture present in the media.

III. B. SMEGMÆ.

Ordinary broth.—Light precipitate at bottom of tube. Heavy white pellicle completely covers the surface of the tube and adheres to side of glass. From this surface numerous thread-like particles hang down into the media or are attached to the sides of the tube, resembling a spider's web in appearance. No clouding of the media.

Glycerin broth.—Same as last media, except that the growth is heavier.

Glycerin agar.—The whole surface of media covered with a thin, whitish growth, showing slight wrinkling. Borders are not sharply defined. Surface of growth nonglistening and dry in appearance.

Plain agar.—Light-yellow growth covers the whole surface of media, borders poorly defined, irregular in outline, surface dry, nonglistening in appearance. Growth is closely adherent to the media, above the level of which it is only slightly raised.

Nutrient agar.—Growth is identical in appearance to that noted on plain agar, except that it is somewhat heavier.

Dorsett's egg media.—Growth of a bright, golden-yellow color, spreading over whole surface of media. Surface of growth is dry, smooth, nonglistening, and shows no tendency to wrinkle.

Potato.—The growth has spread beyond the path of the needle stroke. In the younger portion of the growth it is of a light-creamy, yellow color; in the older portion of a golden-yellow color. Growth composed of numerous, largely raised colonies which, by coalescing, give the surface an irregular appearance. Borders not very well defined. No wrinkling of surface, which is dull and lusterless.

Dunham's peptone.—The only growth that has occurred in this media shows as a light flocculent precipitate at the bottom of the tube.

Glucose broth in fermentation tubes.—A heavy yellowish pellicle covers the surface of the media. Beneath this is a thick, tenacious precipitate, confined to the aerobic portion of the tube. No gas is produced.

Lactose, mannite, and saccharose broth in fermentation tubes.—Identical with glucose broth.

Blood serum.—Growth spreads to border of media, of yellowish color, with sharply defined, regular borders. Surface moderately

dry, smooth, nonglistening, without showing tendency to wrinkle. The media is not liquified.

Serum reactions.—The serum of the horse, mentioned before as being immunized against “B,” “F,” “G,” and “H” “strains” of *B. lepræ*, does not clump, in any dilution, Moeller’s grass bacillus, *B. margarín* or *B. smegmæ*.

SUMMARY.

I. There is no appreciable difference between the individual cultures of the six above-described “strains” of *B. lepræ*.

II. No very marked cultural differences exist in any of the above nine organisms (the six “strains” of *B. lepræ* and three other acid-fast organisms). Slight differences do exist, but it is doubtful whether they are of practical importance as a sure means of distinguishing the organisms one from another, especially as these differences vary from time to time, depending on the media employed, its reaction, its moisture, and other conditions that we do not understand.

III. *B. margarín* especially resembles in its purely cultural peculiarities the cultures we have of *B. lepræ*.

IV. The serum of a horse that has been immunized to four “strains” of the *B. lepræ* strongly clumps all of our organisms, but fails entirely to clump the grass bacillus of Moeller, *B. margarín* and *B. smegmæ*, thus tending to prove that the organisms we have isolated from lepers are different from each of the known acid-fast bacilli tested.

CONCLUSIONS.

I. That by the method of Clegg it is frequently possible to grow an acid-fast bacillus morphologically similar to the leprosy bacillus in tissue from the tissues and organs of lepers.

II. That by heating, in the manner indicated by Clegg, a mixture of the cholera and amœba symbiants and the multiplying acid-fast organism it is possible to isolate this acid-fast organism in pure culture.

III. That this acid-fast organism from lepers resembles in cultural peculiarities other members of this group, represented by *B. margarín*, *B. smegmæ*, and the grass bacillus of Moeller, but that serum tests are capable of demonstrating that a difference exists between the organisms we isolated and the three well-known bacilli mentioned.

IV. That up to the present time, the only evidence there is that the acid-fast organism we have isolated is *B. lepræ* is the frequency with which these bacilli can be grown from leprosy tissue, its mor-

phology and acid-fastness, and the fact that it is neither *B. margin*, *B. smegmæ*, or the grass bacillus of Moeller, three common saprophitic acid-fast organisms.

V. That while the above data do not constitute scientific proof that our cultures are *B. lepræ* any more than it has ever been absolutely proven that the acid-fast bacillus found in lepromata is the bacillus of leprosy, nevertheless the latter is no longer doubted, and we feel that the former will soon be, if it is not now, almost as well established.¹

¹ In a future publication we hope to include the effects of chemical and physical agents on our organisms.

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ATTEMPTS AT SPECIFIC THERAPY IN LEPROSY.

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INTRODUCTION.

Of the many remedies that have been tried for leprosy there exists a group which may be set aside from the remainder and considered as attempts to secure an artificial immunity to this disease in persons already infected with it. For example, as will be seen in the literature to follow, some experimenters have tried tuberculin because of the fact that lepers reacted to this substance, apparently quite similarly to the way in which cases of phthisis reacted to the same substance; as patients with the latter disease were, it was believed, sometimes benefited by this substance, it was natural to suppose that some "group reaction" might be secured in persons infected with this analogous organism and a similar benefit secured in leprosy.

It was also noted that when potassium iodide was given to lepers a similar reaction was produced in them as that caused by tuberculin, and it was thought, therefore, that by stimulating cellular activity in some unknown way it might be possible that this agent set free a certain amount of toxin from the leprosy lesions. If such was the case, it was hoped that this might produce an immunity in the patient. Or, again, as will be seen, several investigators have attempted by the injections of the blood of lepers (or with more understanding of the subject, have injected the juices of the nodules of lepers) into horses, hoping thereby to produce a serum, which would be of benefit to patients suffering from this disease. Still others have by certain means separated the leprosy bacillus contained in the tissues of lepers from the body fluids and cellular agents, and administered these bacilli in the form of a vaccine to cases of leprosy. In doing this they practically but repeated what has been tried with artificial cultures in the therapy of other diseases, and in the

state of knowledge at the time it was used this procedure appeared to be entirely rational; its drawbacks, however, were obvious—the difficulty in getting a sufficient amount of leprosy material and the difficulty in securing a considerable number of washed bacilli from such tissue. Yet up to the time Clegg grew this organism on artificial media it was the only way that a “vaccine therapy” could be tried.

With the successful cultivation of the bacilli of leprosy, it was natural that those persons having cultures of this organism should carry forward the same line of investigation that Koch and others had carried out in tuberculosis.

Whitmore and Clegg, acting on this idea, immediately tried a vaccine (as well as certain extracts prepared from the same bacilli) on a number of lepers in Manila, but their results were negative.

As soon as Currie, Brinckerhoff, and Hollmann, working in this laboratory, had succeeded in confirming Clegg’s cultural work by isolating the bacillus of leprosy, they began most of the experiments which are given in this bulletin, not knowing at that time that Whitmore and Clegg were just completing a similar line of work in Manila. Upon the latter gentleman’s transfer to this station’s force, we learned for the first time of Whitmore and Clegg’s therapeutic experiments and of their failure to produce beneficial effects with vaccines, etc., prepared from their cultures, but as we had carried our experiments on for some weeks at that time we decided to continue them. As will be seen further on in this bulletin, our work along this line has resulted in failure to greatly ameliorate the symptoms of leprosy in our patients, just as the experiments of Whitmore and Clegg resulted in a similar failure.

It will be noted, however, that we have also undertaken a somewhat different line of research in addition to the vaccine and tuberculin-like extract therapy, and we hope to be able to report on this work in a reasonable time. At present, although we give the data covering this latter work as far as we have carried it, we do not consider that we have completed our tests with the serum of a horse, previously immunized or in progress of immunization to our bacilli, nor are we satisfied with the small amount of data we have secured on the effect on patients of small doses of live cultures or of the use of the alcohol-chloroform soluble fatty extract of our bacilli.

REVIEW OF LITERATURE.

THE TREATMENT OF LEPROSY WITH TUBERCULIN.

Among the several attempts that have been made at what might be termed specific therapy in leprosy, Koch’s old tuberculin has been employed chiefly during the time when that substance had its first reputation as a beneficial agent in the treatment of tuberculosis.

The resemblance of the bacillus of leprosy and that of tuberculosis naturally directed the attention of investigators at the time mentioned to the use of this substance in leprosy, as the following literature will indicate:

Danielssen (1), 1891, injected tuberculin into 14 lepers in doses of 0.001 to 0.320 grammes. He found that this substance when thus administered, caused both general and local reactions in from 12 to 72 hours after injection. He considered that the ultimate effect of this substance on lepers was to make their condition worse.

Goldschmidt (2), 1891, first experimented on 5 cases and later on 11 cases of leprosy. These patients received regular doses of Koch's old tuberculin. Most of his cases reacted to the substance injected. This author at first felt hopeful as to a final cure of leprosy by the use of this agent, but further experiments showed him that the patients' condition remained stationary or grew worse.

Truhart (3), 1891, administered tuberculin to six lepers. He found that tubercular cases reacted more than mixed or nerve cases did. He noted that leprosy ulcers healed promptly under this treatment.

Babes and Kalindero (4), 1891, urge the greatest caution in the use of tuberculin in lepers. Among their 11 cases that received this substance, they noted twice a severe and prolonged reaction setting in after injection of 0.8 milligrammes of tuberculin. The general effect was so severe as to threaten the life of the patients, while accompanying this there were reactions about the nodules.

Babes and Kalindero (5), 1891, conclude that lepers react to tuberculin in the same manner that tubercular patients do, except that larger doses are required.

Babes (6), 1891, states that in his experience lepers, at least under certain circumstances, react much stronger to tuberculin than tubercular patients do; this is especially true when the patient is young.

Kalindero and Babes (7), 1891, cite some observations made in the treatment of leprosy by tuberculin, and reached the conclusion that after three months' treatment all lepers showed improvement in their local symptoms. This local improvement did not, however, progress to a complete cure.

Editor, *Lancet* (8), 1892, cites the experience of Poupinel de Valence, Danielssen, Loft, Babes and Kalindero, Colcott, Fox, Cheyne, Powell, Morrow, Goldschmidt, Cantlie, Abraham, Crocker, and Hunter, in the use of tuberculin in leprosy. De Valence considered that improvement resulted from its use and recommended its further trial. Others' experiences are not so favorable, however, and a few failed to observe even the febrile reactions reported as following the administration of this substance.

Thin (9), 1893, refers to Danielssen having employed tuberculin in lepers and states that the latter noted the presence of bacilli in the blood of patients after receiving injections of this substance.

Arnaud (10), 1896, treated a leper with tuberculin injections, which caused an apparently dangerous general reaction, accompanied by the softening and disappearance of nodules. Improvement resulted and continued for two years after the administration of the treatment.

See (11), 1902, employed Koch's old tuberculin in lepers and secured general reactions, some of which cases were afterwards necropsied, which examinations showed that these patients did not suffer also from tuberculosis. This answered the objections raised by Arning and Brieger, namely, that lepers reacted to tuberculin because they were also infected with tuberculosis.

Lie (12), 1904, states:

The more I see of the course that leprosy takes, the more I am of the opinion that the effect of tuberculin upon leprosy should be made the subject of renewed experiments, as it seems by no means impossible that favorable results might thereby be obtained.

Lie (13), 1905, is of the opinion that of the numerous remedies, recommended for the treatment of leprosy, tuberculin is one which deserves greater attention and further trials. He considers that small doses offer the greatest hope, and that a careful study of such dosage is important.

Brinckerhoff (14), 1908, employed Moro's "Percutaneous" test on 12 lepers, and secured reactions in 5 of these. Of these 5 positive reactions, 1 is noted as "prompt, marked," while 4 are noted as "delayed, slight." He concludes, in part, as follows:

The fact that lepers react to cutaneous inunction of a tuberculin salve may be taken as additional evidence of the chemical nearness of the product of the lepra and tubercle bacilli, and support the suggestion already made that tuberculin be given another trial in the therapeutics of leprosy.

Slatineano and Danielopolu (15), 1909, state that lepers react to tuberculin only when they are also tuberculous.

Babes (16), 1909, replies to Slatineano and Danielopolu's article, just quoted, and emphasizes his views that lepers react to tuberculin without being tuberculous, and that this reaction runs a different course. He further claims that in his experience the use of small doses of tuberculin, combined with chaulmoogra oil, effected a remarkable improvement in several cases of leprosy.

Campana (17), 1909, injected a leprous nodule with Koch's old tuberculin and describes certain histological changes that resulted in the nodule referred to.

Nicolle (18), 1909, refers to the well-known fact that lepers react to tuberculin when that substance is injected hypodermically. With

this in view, he used van Piquet's method, as well as Wolff and Calmette's method of administration, but no local reactions were produced.

Slatineano and Danicopolu (19), 1909, state that of 29 lepers that were given Koch's old tuberculin by hypodermic injection, 13 reacted, and of those that did not react, several showed illness after the injection, such as vomiting, headache, accompanied by a drop in temperature to 35° C.

Of 24 lepers, 13 showed positive conjunctivitis when tuberculin was placed in eyes, and these were the same patients that had reacted positively to tuberculin.

We close this review of some of the literature on the use of tuberculin in leprosy, with the statement that this station has employed this agent in the treatment of eight cases of leprosy during a period of several months, without noticing any benefit from the use of this substance. We gave doses of from 0.0001 to 0.00142 milligrams.

THE USE OF IODINE PREPARATIONS IN THE TREATMENT OF LEPROSY.

These preparations have long been known to cause both general and local reactions when administered to lepers. The reason for this phenomenon is not understood, but it seems probable that it is in some way connected with the stimulation of cellular activity, bringing about an absorption of bacillary products, and on this hypothesis may fairly be considered as an attempt at specific therapy.

Among the many that have investigated this subject may be mentioned the following persons:

Danielssen (20), 1886, used potassium iodide quite extensively in the treatment of leprosy and as a diagnostic means in that disease.

Arning (21), 1886, speaking of his experiences at the leper settlement at Molokai states that "iodide of potassium failed entirely in my hands."

Fitch (various reports to the president of the board of health of Hawaii, 1882-1884) used potassium iodide in the treatment of leprosy without any notable results.

Neisser (25), 1897, states that of all the known remedies recommended for leprosy, he expects more from iodine than any other, and refers to Danielssen's results with the use of this remedy, and also to the peculiar reaction which lepers show, even after small doses are given them. He mentions euphene and iodoform, as well as the potassium salt, and thinks that further experiments of this kind may yet lead to a successful mode of treatment.

Wolff (26), 1897, discusses the effects of potassium iodide in leprosy, mentioning febrile reactions, disappearance of old and reappearance of new nodules. He states that during the fever, caused by

the administration of this drug, lepra bacilli appear in the blood of the patient. He considers that the drug has also diagnostic value.

Lie (27), 1900, reports on the use of "europheue" (an iodine preparation) in the treatment of leprosy. He treated three cases with this agent without favorable results.

Babes (28), 1901, mentions the use of iodine preparations in leprosy and states that the general conditions of the patients apparently improve under its employment.

Leredde and Pautrier (30), 1903, mention the diagnostic value of iodine in leprosy.

Lie (31), 1904, believes that among the remedies recommended for the treatment of leprosy potassium iodide is one that deserves greater attention. He suggests the use of small doses of the drug.

Siebert (32), 1905, discusses the reaction of lepers to iodine preparations and states that this reaction resembles that of tuberculin, only the reaction produced by the former substance is not so constant as that obtained with tuberculin. He states further that the explanation of this reaction is not possible at the present time; nevertheless the possibility of beneficial results from these reactions is such as to make the drug worthy of further trial.

This author treated 12 cases with potassium iodide, and of these 2 showed no reaction to the drug, even in doses of 5 grams a day. The other 10 cases reacted to varying doses: thus one patient reacted to a dose of 0.2 grams, while others required 2 or 3 grams before the reaction resulted, and still others larger doses (3 grams, repeated over a period of several days). He mentions some improvement in one of the cases that received this remedy for one and one-half years.

Diesing (33), 1906, recommends the use of a 30 per cent emulsion of iodoform in olive oil by subcutaneous injection. The same author treated three cases with this mixture, and states that it has been further tried at the leprosarium at Memel, at which latter institution one case receiving this mode of treatment has shown remarkable improvement.

Diesing and Dula (34), 1906, treated lepers with a 20 per cent emulsion of iodoform in olive oil and painted the lepromata with tincture of iodine. They state that favorable action can not be expected from this treatment until it has been employed for a long period of time.

Diesing (35), 1907, again refers to the treatment of leprosy with the subcutaneous injection of iodoform suspended in olive oil and states that in his experience all mild, uncomplicated cases and a large percentage of severe cases were cured by this treatment. In most cases, he states, a month's treatment completes the cure. He cautions, however, that organic diseases of the brain, leukemia, and cardiac lesions contraindicate the use of this remedy.

Marchoux and Bourret (36), 1909, state that the iodide reaction in lepers is always accompanied by the destruction of a large number of lepra bacilli, which, under the action of this drug, lose their acid fastness.

Sorel (37), 1909, being interested in the report of Marchoux and Bourret on the effect of iodides in leprosy, and reasoning by analogy from a similarity of the two diseases, employed this drug in patients suffering from tuberculosis and found that the downward course and spread of the latter disease was hastened by the use of iodine preparations. He thinks that this may be due to the active phagocytosis.

To the above literature we may add a summary of the experience at this station in the use of iodine preparations on some of our patients. In most instances we found that severe febrile reactions follow the administration of 2 or 3 grams of the potassium salt, and such reactions were accompanied by hyperemia of the leprosy nodules of the skin. There were some exceptions to this, however, for example, in one well-developed and progressive case of nodular leprosy, we failed to produce febrile reactions or any disturbances, even when 6 grams of potassium iodide were given at a single dose; and again, in another case, which reacted strongly to a dose of 2 grams, an apparent immunity to the drug later developed, so that at the end of a few weeks 30 grams daily failed to cause any reaction whatever. In a third case of early nodular leprosy, the patient was placed on rapidly increasing doses, but he experienced no reaction until a daily dose of 33 grams was received.

In a limited way we have tried subcutaneous injections of iodoform emulsion in olive oil, solutions of potassium iodide by mouth, and inhalations of from 15 to 30 minims of ethyl iodide. It is interesting to note that in the two cases in which the last-named substance was tried, severe febrile reactions invariably occurred a few hours after this drug had been inhaled. Our employment of the iodides has not extended over a sufficient length of time to form any opinion as to their value, if any, in the treatment of leprosy.

THE TRIAL OF CARRASQUILLA'S SERUM IN THE TREATMENT OF LEPROSY.

Following the success met with in the use of diphtheria antitoxin, it was natural that attempts should be made to obtain a curative serum for other diseases, and the following review shows that leprosy was among the diseases that did not escape such efforts. Viewed from the light of our present-day knowledge, there was nothing in Carrasquilla's serum that could be expected to offer the slightest hope as a curative agent. Nevertheless, the attempts are worthy of recording for their historical value, and possibly also to show the patient consideration that is apt to be accorded to the most shadowy claim of a cure for leprosy.

The following review contains the better known publications on the manufacture, trial, and final rejection of this serum:

Carrasquilla (38), 1896, at a meeting of the Medical National Academy of Colombia, reported on what he claimed to be a complete success in the treatment of 15 lepers by means of a serum which he had prepared. At this meeting Carrasquilla did not describe the method he employed to obtain this serum.

Fournier, Besnier, Roux, and Hallopeau (40), 1897, investigated the claims of Carrasquilla and reported that in their opinion there was no improvement in the patients that received this treatment, and that therefore the claims of Carrasquilla were without foundation.

Carrasquilla (41), 1897, reports on the manufacture of his serum and the results obtained therewith. He draws 250 c. c. of blood from young lepers, allows it to coagulate, and pipettes off the serum. He states that this serum varies from a perfectly clear, odorless fluid through various grades of cloudiness to a greenish fluid with an offensive odor. He further states that this variation in the serum's properties was due to the condition of the patient at the time the bleeding was made, apparently not considering that it might have been due to the amount of bacterial contamination that had accidentally taken place.

At intervals Carrasquilla administered from 50 to 150 c. c. of this serum of lepers to healthy horses, with the result that the animals became ill and often developed abscesses. After the horse had recovered from its illness produced by the injection of the human serum (and possibly its contained bacterial contamination) the animal was bled, its serum collected in the usual manner and given to lepers.

Lepers that received this treatment had, following their injections, a chill, succeeded by a temperature of from 38° to 39° C., occasionally as high as 41° C., and this reaction was followed by recovery of the patient from leprosy.

Buzzi (41), 1897, reports on the results which he has obtained in a 15-year-old boy treated with Carrasquilla's serum. Following the injection there was a local reaction at the site of the needle puncture, accompanied by collapse and chills, lasting over a period of days after the injection. During this illness, apparently produced by the serum, his leprosy lesions showed reddening, swelling, and softening, followed by absorption or discharge.

Ashmead (43), 1897, cites Havelburg, Goldschmidt, Hansen, and Alvarez as being skeptical as to the utility of Carrasquilla's serum. He further quotes Roman and Rojas as believing that this serum might have value.

Barillon (44), 1897 (under the direction of Carrasquilla), manufactured a similar serum and tried it on 5 lepers. He succeeded in producing fever and serious general symptoms in his patients, but they failed to improve in so far as their leprosy was concerned.

Polakowsky (45), 1897, reviews the experiences of those who have employed Carrasquilla's serum.

"Discussion," Lepra Conference, Berlin (47), 1897: At this discussion Alvarez thought he had observed improvement in 2 out of 14 cases that had received Carrasquilla's serum, and Arming claimed to have secured a distinct influence and temporary improvement by using this serum. The other persons that took in this discussion were in accord that this serum was noneffective in the treatment of leprosy.

Carrasquilla (48), 1898, again refers to his treatment and is enthusiastic in its praise.

Atherstone and Black (49), 1898, report on the treatment of 2 cases of leprosy with Carrasquilla's serum, as well as Herman's serum. They state that "considering the improvement which any leper may show spontaneously, and further the psychical effect of such treatment, they are of the opinion that the slight objective change and the improved general condition of the patient furnish no positive proof that this agent is of benefit."

Dehio (51), 1898, reports on the treatment of lepers under his care with Carrasquilla's serum. In his experience, extending over a period of two and one half months, he obtained no results whatever from the use of this substance, and believes that the reactions secured by Carrasquilla were due to "einfache Proteinwirkungen."

Grunfeld (52), 1898, treated 4 lepers with Carrasquilla's serum, and reports as a result of this treatment that the nodules decreased in size, the facial infiltration lessened, and ulcers healed.

Tidswell (54), 1900, treated 2 lepers with this serum with entirely negative results.

Thompson (55), 1900, reviews the reports of others who have tried this serum, and these reports, coupled with his own experience, leads him to believe that there is no evidence of the value of this treatment; and that, further, Carrasquilla "seemed to have been unfamiliar with the common methods and precautions ordinarily employed in the manufacture and use of serum, as well as some of the usual effects of the administration of horse serum to man."

Medina (56), 1910, states that Carrasquilla's serum sometimes induces marked febrile reactions, accompanied by headache, etc., and that cases that thus reacted showed marked and apparently permanent improvement. On the other hand, cases which did not have this febrile reaction after the injections showed no improvement. The author states further that arrangements have been made to continue the use of this substance on a large scale, and that at present 120 patients are receiving this treatment.

Morrow states that Putnam of Colombia (Twentieth Century Practice of Medicine, vol. 18, p. 588) used Carrasquilla's serum on 40 cases of leprosy without success.

SERA OTHER THAN CARRASQUILLA'S THAT HAVE BEEN TRIED IN THE
TREATMENT OF LEPROSY.

Babes (57), 1893, immunized animals with avian tuberculosis and injected the serum from such animals into lepers. As a result of this treatment he noticed increase in weight and general well-being, but no changes in the leprous lesions.

Abraham and Herman (58), 1897: Following correspondence with Carrasquilla, Herman undertook the manufacture by a method entirely different from that employed by Carrasquilla; that is, he took a leprous nodule and subjected it to pressure, thereby expressing the fluid contents of the nodules, and it may be presumed he also expressed many lepra bacilli. He then diluted this fluid with normal salt solution and gave it to a horse by hypodermic injections, several cubic centimeters of this serum being given the animal every week or two for a period of four and one-half months. In all, the horse received 10 injections; very slight or no reactions occurred in the animal after these injections. Four weeks following the ninth injection the horse was bled and the serum collected and preserved with thymol. After the tenth injection the animal was again bled and more serum collected.

This serum was then administered by Abraham to 2 cases of leprosy; and on Robben Island it was administered to other cases, but of these, with the possible exception of 1 patient, no favorable results were noted from the use of this substance.

Laverde (59), 1897, secured leprous nodules and used the tissue fluids of these to inoculate goats and donkeys. These animals were afterwards bled, their sera obtained and administered to patients suffering from leprosy.

The patients receiving this treatment showed febrile reactions, malaise, and other general disturbances. Following these reactions, the author states, marked improvements occurred in the leprous lesions and a disappearance of anæsthesia was noted. He continued the treatment for periods varying from three months to a year, and continued to produce improvement in his 60 patients up to the time of writing; in fact, he reports that 6 of these 60 patients have been cured.

Babes (60), 1899: In this article Babes refers to the bacillus which he cultivated and at that time believed to be *B. lepræ*. He prepared an extract (similar to the method used by Koch in the preparation of tuberculin) from this organism, which he had isolated from lepers, and administered it to certain patients suffering from leprosy. This treatment caused febrile reactions in the patients. He then attempted to immunize certain animals against this organism and later administered their serum to lepers. He expected to report on the results at some future date.

RATTLESNAKE VENOM IN THE TREATMENT OF LEPROSY.

This unique mode of treatment in leprosy apparently had its origin in the popular belief that exists in certain countries, that lepers that had been bitten by a poisonous snake and recovered from the effects of the bite often also recover from leprosy.

Carreau (61), 1892, refers to a case reported by Dechambre, in which a leper was bitten by a poisonous snake and recovered from both the snake bite and leprosy. Carreau, acting on the supposition that the supposed beneficial effect of snake bite on leprosy was due to hemolysis, administered poisonous doses of potassium chlorate, hoping thereby to produce hemolysis in lepers with somewhat less danger than by means of snake venom.

Marcoudes de Moura (62), 1900, speaks of a superstition that exists among the country people of Brazil, viz, that if a leper is bitten by a rattlesnake and does not die from the effects of the bite he will recover from his leprosy. This investigator attempted to confirm this by artificial administration of rattlesnake venom intravenously, and reports that under the influence of this treatment leprosy nodules and anæsthesia disappear, and suggests that more success might be met with if the venom of the rattlesnake was given mixed with the antivenom serum of Calmette.

Lewin (63), 1900, reports unfavorably on the use of rattlesnake venom in the treatment of leprosy.

Marcoudes de Moura (64), 1902, reports further on the use of rattlesnake venom in the treatment of leprosy, and states that he has used it in 15 patients and has been led by the results he has obtained so far to believe that this treatment offers hopes of a cure for leprosy. He promises to furnish a more complete report at an early date.

Goldschmidt (65), 1902, calls attention to the fact that in 1892 Carreau called attention to the beneficial influence of snake venom in leprosy.

Morrow (66) quotes Laverde as stating that lepers in Colombia purposely allowed snakes, scorpions, centipedes, etc., to bite them, but the only definite information on this subject as to the effects secured was that the experiment often produced fatal results.

THE USE OF ANTIVENENE IN THE TREATMENT OF LEPROSY.

Dyer (67 and 69), 1897 and 1905, after mentioning the different sera that have been applied in the treatment of leprosy by Carrasquilla, Babes, Abraham, and Herman, refers to a publication of Carreau (*Contribution au Traitement de la Lèpre, Jamaica, textbook, 1892*), and further refers to a case reported by Winslow, in which a leper was bitten by a rattlesnake with a fatal result.

Impressed by the article of Carreau, Dyer conceived that a possible benefit might result from the use of Calmette's "antivenene," and therefore placed 5 cases of leprosy on this treatment. Four of these patients, Dyer reports, showed marked improvement, and in 1 case there was a disappearance of the leprosy lesions. He states that it is his purpose to continue these experiments, so satisfactorily begun.

Woodson (68 and 68a), 1899, reviews Dyer's report on the use of antivenene in the treatment of leprosy, and employs the same treatment himself on 1 case of leprosy. This patient is reported to have shown improvement. Woodson doubts, however, that this improvement was due to the serum alone, as the patient also received "Hoang-nan."¹

THE LEPROLIN OF ROST IN THE TREATMENT OF LEPROSY.

In 1905 considerable interest was aroused among leprologists by the claim of Rost to have grown the bacillus of leprosy on salt-free media, and that from these cultures he had produced a substance that bore the same relation to leprosy that tuberculin did to tuberculosis. The following review gives the most important literature on the use of this substance in leprosy:

Rost (70), 1905, claims to have grown the bacillus of leprosy by the use of various kinds of salt-free media. From his cultures he prepared a substance, which he believes to be analogous to Koch's tuberculin in tuberculosis, and administered this to lepers. This treatment, he claims, caused reactions in his patients, followed by an improvement in their conditions.

Rost (71), 1905, reports again on the treatment of leprosy with his tuberculin-like substance, which he terms "leprolin," and states that patients that received his substance have return of perspiration in areas which had lost this function. There is also return of sensation in anæsthetic areas, accompanied by gain of strength, healing of nodules, etc.

Editor, *Lancet* (72). 1905, speaks of the use of leprolin of Rost in the treatment of leprosy, and states that the three patients that have received this treatment in India have been declared practically cured, while other patients similarly treated have shown improvement.

Semple (73), 1905, investigated the claims of Rost and concludes that—

1. Capt. Rost has failed to demonstrate a growth of the leprosy bacillus in his media at Kasauli.

2. The material used to inoculate the media was without doubt taken from leprosy cases and contained leprosy bacilli in large numbers.

3. The leprosy bacillus has not yet been cultivated, and the preparation of leprolin is for the present an impossibility.

¹ *Strychnos gaultheriana*, natural order Loganiaceæ.

4. Defective technique in the preparation of his media and in eliminating subsequent contaminating growths are the probable causes which have given rise to Capt. Rost's mistakes.

De Beurmann and Gougerot (76), 1909, studied the action of leprolin prepared by Rost, and affirm that it produces febrile and general reactions in persons suffering from leprosy, as well as changes in their lesions. On the other hand, healthy persons, they claim, do not react to this substance; they believe that the substance may have diagnostic value.

NASTIN IN THE TREATMENT OF LEPROSY.

Deycke-Pascha and Reschad-Bey (or the first author alone), in numerous articles (77, 78, 79, 80, 82, 83, 84), describe their work which led up to the preparation of a substance that they call "nastin," or "nastin-B," and which they employed in the treatment of leprosy.

Stated briefly, these two investigators succeeded, by placing leprous material in saline solution and incubating this for a long period, in obtaining a growth of an acid-fast organism from a severe case of leprosy. They did not consider that this organism was the bacillus of leprosy, but probably that it was an "atavistic throwback" of that organism. Later, however, they concluded that it was a streptothrix. From this organism they then prepared a killed suspended culture (vaccine) and administered it to the patient from whom they had isolated the organism in question. This patient reacted severely to the injection of this vaccine, and following these reactions there was an improvement in his condition.

Believing that it was probable that the good effect noted in this patient was due to immunization with the acid-fast constituents of this organism, they abandoned the use of the vaccine and turned their attention to the isolation of this acid-fast substance. After many efforts on their part they succeeded, by fractional extraction with ether, in securing a number of chemical products from the organisms that they were dealing with. Some of these they rejected as useless and possibly injurious, and finally isolated pure a fatty substance, which they call "nastin."

Still later in their work they thought that this substance "nastin" would be improved by mixing it with benzoylchloride, and the new product thus formed they called "nastin-benzoyl" or "nastin-B." This latter substance, they claim, can be given to lepers without causing the severe reactions that nastin alone is said to produce. They report that 73 out of 81 cases of leprosy have shown improvement under the administration of nastin-B, but in another article they call attention to the uselessness of treating far advanced cases with this agent.

Thompson (81), 1907, refers to the claims of Deycke-Pascha and Reschad-Bey.

Lenz (85), 1909, obtained no marked improvement in cases treated by him with nastin.

Kupffer (86), 1909, states that he has secured some very good results from the use of nastin alone, and recommends that this agent be employed in conjunction with chaulmoogra oil.

Much (87), 1909, states that patients suffering from tuberculosis react to nastin and, vice versa, lepers react to tuberculin, and also that tubercular patients react to the fatty substance of tubercle bacilli, which he calls "tuberkulonastin."

Rodrigues (88), 1909, treated 23 lepers with nastin and reports favorable results, such as healing of ulcers, loss of anæsthesia, and improvement in general condition, but none of his patients have been completely cured.

Smith and Bisset (89), 1909, treated 6 patients with nastin with such favorable results as the healing of ulcers and the loss of anæsthesia.

Thompson (9), 1909, states that patients that received nastin react both locally and generally, and that these reactions demonstrate the activity of nastin, but of the 2 patients treated by him with this substance 1 grew worse and the other's condition remained stationary.

Teague (91), 1909, treated 4 cases of leprosy with nastin for a period of 9 months without any effect.

Davidson (92), 1909, reports that all of the cases of leprosy that he has treated with nastin have improved under its use.

Peiper (93), 1909, employed nastin in the treatment of 2 lepers with absolutely negative results.

Raschid (94), 1909, reports the improvement of 2 lepers after treatment with nastin.

Williams (95), 1909, publishes a letter that he has received from Deycke, describing the method employed in the manufacture of nastin, together with its use and effects in leprosy. Williams then speaks of his own experience with the substance.

Brinckerhoff and Wayson (96), 1909, employed nastin-B on 6 cases of leprosy, for periods of time varying from 5 to 15 months, without securing any notable results. Their conclusions were as follows:

1. In our hands the administration of nastin to 6 cases of leprosy gave slightly encouraging results in 2 cases. In 1 of these the lesions decreased in extent and took on a focal character. In the other case a tubercle disappeared during the treatment.

2. Four cases seemed unaffected by the treatment, even when persisted in for over a year.

3. Constitutional reactions were only seen when the dosage was large. No local reaction or puriform softening of tubercles was observed.

LOCAL TREATMENT IN HOPES OF PRODUCING GENERAL SYSTEMIC EFFECTS.

Several investigators have attempted to employ what was obviously only a local treatment of the skin lesions of leprosy, hoping thereby not only to benefit the lesions actually treated, but, by the stimulation of cellular activity in the region of the lesion, to cause an absorption of lepra bacilli or their products, and possibly bring about an active immunity to the infecting organism.

It is impractical to review all the attempts of this character, especially those in which various stimulating ointments have been employed (such as chrysarobin and pyrogallol, used by Unna and others), but the following literature contains the recorded experiences of several authors who have tried what appeared to logically offer the greatest hopes in this direction.

Belot (97), 1904, reviews the work that has been done up to the time of his writing on treatment of leprosy by means of the X and radium rays. He cites the work of Segueira (1901), and states that under this treatment Segueira's patients' symptoms improved, the nodules softening and partially disappearing. He further cites de la Camp as having tried X rays in leprosy without any noticeable results, and Scholtz as reporting the successful treatment of 2 cases of leprosy by this means. He further cites the work of Oudin (98) in the treatment of leprosy by means of radium rays.

Oudin (98), 1904, reports on the treatment of 2 cases of nodular leprosy with radium rays, and claims that these cases improved.

Lie (99), 1905, states that he is inclined to believe that both X rays and Finsen rays exercise a certain influence on the leprosy process.

Lassar, Siegfried, and Urbanowitz (100), 1905, report on the treatment of 9 lepers by means of the X ray, and state that the results have not been the same in all their cases. From their experience they discourage the use of this treatment in advanced cases, but think that it should be tried further in incipient cases of leprosy.

Wilkinson (101), 1905, reports on the treatment of 13 cases of leprosy with X ray, and reports 3 of these cases as cured and 7 improved, while the other 3 cases remained entirely unimproved.

Heiser (102), 1906, reports the recurrence of symptoms in 2 of the 3 cases of leprosy, supposed to have been cured by Wilkinson (vide supra) by means of the X ray.

Black (103), 1906, states that the utility of the X ray in the treatment of leprosy is very doubtful.

Pasini (104 and 105), 1907, reports on a case of nodular leprosy, treated by him with the X ray and Finsen light. The patient has apparently recovered, and, at the time of writing, eight months after his recovery is supposed to have taken place, there had been no return of symptoms.

Matthews (106), 1908, reports on 7 cases of leprosy treated with the X ray, and, from the results he has obtained in these patients, considers this a valuable therapeutic means in handling this disease.

Heiser (107), 1908, reports on a case of leprosy treated by the X ray. At the time this article was written the patient had apparently recovered. (We have been informed since, however, that this patient afterwards suffered a relapse.)

Bulkley (108), 1909, refers to the work of Heiser and Wilkinson on the use of the X ray on lepers in Manila.

MISCELLANEOUS VACCINES EMPLOYED IN THE TREATMENT OF LEPROSY.

Campana (109), 1882, inoculated 2 lepers with erysipelas without any beneficial results.

Havelburg (110), 1891, inoculated lepers with cultures of the streptococci of erysipelas; reaction was so severe that inoculation had to be discontinued. He then tried the same method plus antistreptococci serum, but neither of these treatments were beneficial.

Alvarez (111) employed injections of the *Bacillus prodigiosus* alone in lepers without any favorable results.

Chapin (112), 1899, used Coley's toxine (suspended cultures of the streptococcus of erysipelas and the *B. prodigiosus*). The patients were not benefited by this treatment.

Ashmead (113), 1908, writes of the subcutaneous injection of yeast cells as a treatment for leprosy.

THE TREATMENT OF LEPROSY BY THE EMPLOYMENT OF INJECTIONS OF SUSPENDED LEPRO BACILLI.

Scholtz and Klingmuller (114), 1900, expressed the tissue juice from lepromata and administered this fluid to lepers. Their object was to secure a tuberculinlike substance. It may be presumed, however, that such a fluid would also contain many lepra bacilli in suspension, and this treatment they employed may therefore be considered to have been a lepra vaccine. So far as we know, this is the first attempt of this kind in the treatment of leprosy.

Castellani (115) (date unknown): This author is said to have vaccinated human lepers with emulsions prepared from their own tissues.

Woolley (116), 1907: The original article is inaccessible to us, but it is stated that he proposed the treatment of leprosy by the injection of graded doses of lepra bacilli killed by gentle heating. He obtained his suspensions from ground-up lepromata. He reports the beginning of treatment of 1 case, but was unable to continue the treatment.

Nicholls (117), 1908, prepared a vaccine, as follows: A skin incision was made down to the nodule, which latter was removed, together with a quantity of the surrounding subdermal tissue. This

tissue was placed in a tube of glycerin broth and incubated for a fortnight. The broth and tissue are then placed into a shallow vessel and slowly desiccated. The dried mass was finally powdered in an agate mortar, a suspension made, and the bacilli counted by the usual manner of comparison with blood corpuscles, and killed by heating to 60° C. He believed that during the time of incubation the bacilli multiplied in the tissues.

Nicholls treated a case of leprosy, a patient of Sir Malcolm Morris, with this vaccine, which substance contained 50,000,000 organisms per cubic centimeter. He repeated this injection every 4 days at first, and later every 7 to 10 days. Under this treatment some nodules disappeared and others softened.

Rost (*vide supra*), in employing what he believed to be cultures of lepra bacilli, must have inoculated many lepra bacilli that had been carried over directly from his leprous tissue into the salt-free media he employed, and therefore his "leprolin," being a more or less concentrated suspension of lepra bacilli, may be considered as an example of a vaccine treatment for leprosy.

Whitmore and Clegg (118), 1910: After the latter had grown the bacillus of leprosy and isolated it in pure culture (Philippine Journal of Science, Vol. IV, pp. 77, 403), he and Whitmore prepared a vaccine as follows: A vaccine was made in the ordinary way and standardized to 500,000 bacteria per cubic centimeter. The bacteria in this vaccine showed a great tendency to form clumps on being allowed to stand without shaking. Injections were given once a week, in doses varying from 0.25 to 1 c. c. of this substance. Any increase above this dose produced a local reaction, preventing the absorption of the bacilli, and later an abscess would form at the site of injection.

They treated 11 cases of leprosy in this manner for eight months and 21 cases for seven months. None of these cases showed any improvement, and the abscess production was a serious obstacle to this treatment.

They then employed a glycerin extract made in a similar manner to that prepared by Koch from the tubercle bacillus. They tested lepers with this material to see if they would give an analogous reaction to Von Piquet's skin reaction in tuberculosis, but their results were negative. They then used this glycerin extract in the treatment of the 32 cases of leprosy that had previously received the vaccine. No reaction followed this latter treatment, and there was no improvement. They then made a preparation by emulsifying their cultures of *B. lepræ* in 1:60 aqueous solution of sodium oleate. The bacteria were almost completely dissolved by this fluid. They employed this soapy solution of the lepra bacilli on the previously mentioned patients. Under this last-mentioned treatment 2 of the patients had

a sharp febrile reaction, accompanied by swelling and redness around the leprous lesions. There was no local reaction at the site of injection, however. They continued this treatment for two and one-half months, but the patients showed no improvement under its use.

They then took the spleen of a leper (which organ was rich in lepra bacilli), ground up the tissue, added a 1:60 aqueous solution of sodium oleate, filtered it through cotton, and heated it for one hour at 60° C. This latter was given to the above-mentioned cases, but none of the patients so treated showed any improvement.

Williams (118a), 1911, by the use of ordinary broth and Rost's media, grew several organisms from cases of leprosy, no two of which organisms, however, appeared to be similar, varying from an acid-fast diphtheroid to a streptothrixlike form; and in one case an acid-fast bacillus. He considers it at least probable that the organism believed to have been grown by Rost, the streptothrix grown by Deycke, and the acid-fast bacillus grown by Clegg are the same as his organisms, and all of them pleomorphic forms of *B. lepræ*. His reasons for believing the above, however, are far from convincing.

From this organism, or more probably organisms, he has prepared a vaccine and used it on lepers, producing thereby febrile reactions, accompanied, apparently, by some improvement in some cases.

SPONTANEOUS CURES.

While all attempts to artificially immunize lepers against this disease have resulted in failure, nevertheless it is apparent that in exceptional cases the body itself is capable of establishing a sufficient degree of natural immunity in individuals once infected with leprosy to bring about what appears to be a spontaneous cure. The literature of leprosy contains many such examples; in fact, it is probable that every leprologist of any considerable experience could recall to mind cases of this kind. Some observers have gone so far as to state that it was doubtful whether a person ever had active leprosy more than 15 years, i. e., if he did not succumb to this disease by that time, that the active progress of the disease ceased, although, of course, the damages that had already occurred remain permanent.

Sufficient for the purpose of illustrating this point are the following references bearing on such spontaneous cures:

Cottle (119), 1889; Crespin (120), 1897; Montgomery-Douglas (121), 1903; Tonkin (122), 1905; Dubreuilh (123), 1905; Dyer (69), 1905; Hutchinson (124), 1905; and Kayser and van Houtom (125), 1905.

SUMMARY OF SOME OF THE KNOWLEDGE GAINED FROM THE ABOVE LITERATURE.

In studying the effects of the above-mentioned agents that have been used in the treatment of leprosy, it will be noted that most if

not all of them in the hands of certain observers and in certain cases have caused the patients to experience febrile reactions, followed by softening of old nodules, the reappearance of new nodules, etc. Such effects have often been considered as evidence that the substance administered was specific in its nature, and that the reaction that was obtained was analogous to that obtained in tuberculous patients when given tuberculin.

It appears to us, however, to be extremely doubtful that such conclusions are in the least justifiable, but rather that the mass of evidence we have up to the present indicates that anything that causes disturbances in the metabolism of a leper is often capable of bringing about the febrile and other disturbances mentioned. Similar febrile reactions are noted in lepers, accompanied often by disturbances in old lesions and the reappearance of new lesions, from many causes; not only from the hypodermic injection of the foreign substances, but from as unlike causes as exposure to cold, surgical operation, wounds and injury, pregnancy, etc., all of them causing more or less profound disturbances of metabolism.

For these reasons it seems to us that in treating leprosy and attempting to estimate the value of a remedy errors in judgment are especially liable to occur, and the irregular course of the disease itself further increases this difficulty of determining, after a short trial, the amount of benefit produced by a therapeutic agent.

While on the subject of literature we may mention that we have reviewed many articles bearing on the manufacture and use of various toxines, vaccines, etc., that have been employed in other diseases; but for the sake of brevity, and from the fact that the leading articles on these subjects are usually well known, we have not included these in our list of references. In our work of preparing the extracts of lepra bacilli we have especially followed the work of Koch in the preparation of his tuberculin and the other substances, and have in this connection reviewed, in the original, all of his articles bearing on his work along this line, from the time that he first announced his "old tuberculin" up to the preparation of his "bacillary emulsion." Most of our technique, in the preparation of these extracts, have therefore been but imitations of his work, with such modifications as the difference in the biological peculiarities of our bacilli and the tubercle bacilli seemed to make desirable. Thus, we started by using (like Koch did with the tubercle bacilli) suspended cultures of our organism, but we found, as Koch did with his organism, that such vaccines produced abscesses, or were at least slow of absorption. We then, like he, prepared a glycerin extract by growing our bacilli on glycerin bouillon, concentrating the latter down, and filtering it. Still later we ground our bacilli and centrifugated the mass, throwing down the unbroken, still acid-fast organisms to the bottom of the tube, and

saving the superimposed fluid, analogous to Koch's "T. O.," and by repetition of this process produced the analogue of "T. R." Of this we used very little, however, and next tried the complete grinding up of the bacilli (without separating "T. O." and "T. R." analogues) until no longer acid fast, followed by the collection of this structureless mass and its suspension in saline fluid; this latter corresponded to Koch's "bacillary emulsion," or, as is usually referred to, "B. E."

The use of live cultures and the use of the fatty extract was, of course, a departure from Koch's methods, but was not novel so far as the method is concerned, as live tubercle bacilli have been given to tubercular patients¹ and Deycke has previously used the fatty extract of another acid-fast organism in the treatment of leprosy.

PRELIMINARY WORK.

Before the cultivation of the bacillus of leprosy by the method of Clegg had been effected at this laboratory one of us (D. H. C.) prepared two substances and employed them on lepers. Neither of these substances proved to be of value, but it is considered advisable to mention them here merely as records in the history of the attempts at specific therapy in this disease.

One of these substances was prepared as follows:

Six flasks were chosen, filled with 500 c. c. of glycerin bouillon and sterilized in the usual manner. One of these flasks was inoculated with *B. smegma*, another with one of the acid-fast grass bacilli of Moeller, another with the margarin bacillus, another with the urine bacillus, one with the nasal bacillus of Karlinski, another with an acid-fast bacillus labeled "Lombard's pellagrine" bacillus. These 6 cultures of acid-fast bacilli were allowed to grow for a month at 37° C., when a heavy pellicle formed on the surface of the media. The cultures were then filtered, the pellicle collected and dried. The dried cultures of the 6 organisms were mixed together and ground in an agate mortar until the clumps had been entirely broken up. They were weighed and a 10 per cent suspension made in normal saline solution. These organisms were killed at 70° C. for one hour, and 1 c. c. given intraperitoneally to each of 6 rabbits and 6 guinea pigs. These animals lost weight rapidly and died some six weeks after inoculation. The necropsy on these animals showed a white cheesy

¹ Klemperer ("Experimenteller Beitrag zur Tuberkulose-Frage," Zeitschrift für klinische Medizin, vol. 56, 1905, p. 258) took tuberculous material from cattle (bacillus of bovine tuberculosis), and after passing this through guinea pigs, in hopes of lowering their virulence, administered these live organisms, taken from the guinea pigs, to persons suffering from pulmonary tuberculosis.

Webb, Williams, and Barber (Journal of Medical Research, vol. 20, 1909, p. 1) inoculated 5 tubercular patients with live tubercle bacilli, and these authors quote a verbal communication from Moeller that the latter investigator had inoculated tubercular patients with a culture of human bacilli after the organisms had been modified by passage through a crocodile.

mass in the peritoneal cavity at the site of inoculation. This mass was filled with acid-fast bacilli. As would be expected, the bacilli being dead, there had been no spread of the lesions beyond the site of the inoculation. It was therefore presumed that the animals died of a slow toxemia from the gradual breaking down and absorption of the bacillary bodies. Smaller doses ($\frac{1}{4}$ c. c.) were then given to other laboratory animals of the same species. They became greatly emaciated, but after several months' illness they all recovered.

After these preliminary experiments on animals this suspended, killed, mixed culture was given to 2 cases of nodular leprosy in doses of 1 to 2 minims by subcutaneous injection after diluting with normal saline solution. This treatment was continued over a period of nearly four months.

The injection of this material into the patients caused no local or general disturbances other than a slight redness at the site of injection, which, however, soon disappeared.

Two or three weeks after the beginning of treatment one of the patients had many of his nodules (which had not previously shown any tendency to soften) soften in the center and discharge, leaving round, punched-out, "craterlike" ulcers, surrounded by a rim of firm leprous tissue. At the beginning of treatment it was estimated that there were something over 300 small nodules present over this patient's body, varying in size from that of a pea to half an inch in diameter. At the end of three months' treatment about one-half of these nodules had broken down in the manner described. The patient's weight and general health remained unchanged throughout the treatment. Up to the time of discharge most of the ulcers mentioned remained unchanged, i. e., showed no tendency to granulate over, but a few of them had healed over. During the last two or three weeks this patient was under observation no further breaking down of the nodules occurred. For administrative reasons this patient, together with several others, had to be discharged at this time, so could not be treated any further.

The other patient that received this treatment began to experience the same breaking down of the nodules on their centers that the first-mentioned patient had shown, but in the case of the second patient, after 12 or 15 nodules had thus broken down into ulcers, the phenomenon ceased, and from that time up to the time of his discharge (four months from the beginning of the treatment) there were no changes in either his general condition or his lesions.

It was our intention to continue this form of treatment on other patients, but about this time the work which led to the isolation of *B. lepræ* by Clegg's method changed our plans, and all of our energies were devoted to studying the effect of our newly acquired *B. lepræ* cultures and their products in the treatment of our patients.

The other substance which we referred to was prepared as follows: The six acid-fast organisms above mentioned were grown in the same manner as that described under the preparation of the vaccine just referred to. After being thoroughly dried these organisms were extracted, first with hot alcohol, then with equal parts of alcohol and ether, then with pure ether. These extracts were filtered to remove all suspended matter. The alcohol, ether-alcohol, and ether extracts were then mixed together and evaporated to dryness. The resulting substance was a waxlike material of an orange-yellow color. This was again dissolved in ether and alcohol added to this solution (which partially precipitated it), and to this ether-alcohol partial solution, partial suspension, was added an equal bulk of sterile water. This caused the substance that had been dissolved by the ether to further precipitate in a fine, flocculent mass, which, however, could be shaken to a uniform emulsion. The ether was then evaporated off until only a trace of it remained, and this alcohol-watery suspension, containing a trace of ether (which latter substance is found, even if present in small quantities, to be of assistance in keeping the emulsion from separating), was given to two cases of nodular leprosy. These patients received large injections of this substance for a period of four months without experiencing either general or local reactions; nor was there the slightest improvement in their condition.

PRODUCTS OF OUR CULTURES OF B. LEPRÆ THAT WE HAVE PREPARED AND USED IN THE TREATMENT OF LEPROSY.

I. VACCINE.

We chose young cultures from four to six "strains" (i. e., isolated from as many cases of leprosy) of our organisms that had been grown upon glycerin-agar, rendered just alkaline to phenolphthalein (on a less alkaline media than this the organism appears to be more difficult to emulsify perfectly, tending to remain in small clumps). These cultures were rubbed in normal saline solution and heated to 70° C. for one hour and control cultures taken, which showed the organisms to be dead. As soon as the control cultures were taken one-half per cent phenol was added to the suspension of killed bacilli. We then standardized the organisms in comparison with red blood corpuscles. Later we standardized by comparison with suspensions of known strength vaccines. These vaccines were always freshly prepared at intervals of one or two weeks, as we feared that either the phenol or the action of light might have some deleterious effect on the bacilli. The strength of the vaccine we prepared varied, depending upon our needs; we found that a suspension of 500,000,000 bacilli was a convenient form of stock vaccine, which could be easily diluted to meet the requirements of the case.

In all our subsequent references in this article in which we employ the word "vaccine" the above suspension is meant.

II. LIVE CULTURES OF *B. lepræ*.

We chose a very young culture of the organism which had been grown on glycerin agar. We usually employed the organism we have designated as "H" (isolated from a Hawaiian case of leprosy) for this purpose, but at times we employed three or four "strains" of our organisms, some of them isolated in Hawaii and some of them in the Philippine Islands. In the preparation of these live culture suspensions we took a definite quantity of normal saline solution and added to it a definite number of loopfuls of our cultures. By manipulation this was made into a perfectly homogeneous suspension of the bacilli. We administered 1 c. c. of these preparations at a dose.

III. LEPRATOXINE.

We prepared 2 per cent glycerin bouillon, sterilized it under pressure and rendered it alkaline to phenolphthalein, and inoculated it from the cultures of our organisms, each flask being inoculated from a single "strain." These flasks were kept at incubator temperature from one to three months. From time to time we gently shook the contents of the flask, so as to cause the surface growth to sink to the bottom and thus make room for the formation of a new pellicle. At the end of the time indicated a very heavy growth of the bacilli was present, forming a sediment half an inch or more in thickness on the bottom of an ordinary 1,000 c. c. Koch's flask that contained 500 c. c. of media. In the early part of our work we were undecided as to the best method of killing and extracting these organisms; we at first used only a little more than the minimum amount of heat necessary to kill them, namely, 65° to 70° C. for one hour, thinking possibly that more intense or prolonged exposure to heat might destroy some toxic substance in the organism. With increasing experience, however, it appeared to us that the most marked effects were obtained from the use of extracts prepared by bringing the bouillon culture to a boil and allowing it to remain at this temperature for one or two hours. Still later we found that by subjecting the cultures to 60° C. for three to four days, followed by boiling for one hour, we obtained what appeared to be the most potent extract we had thus far secured, and after reaching this conclusion we experimented no further along this line, but continued this mode of preparation of the extract.

After thus killing and partially extracting the organisms we placed the fluid at from 60° to 76° "vacuum" and evaporated it down until the extract was 50 per cent glycerin, or about one twenty-

fifth of its original bulk. This we then diluted with several times its volume of sterile distilled water, and filtered it through porcelain. After this it was returned to the vacuum and again evaporated down to 50 per cent glycerin. The resulting fluid was dark brown in color, due in part to the beef extract and peptone contained originally in the bouillon; but, besides this, it was evident that a distinctly yellowish shade of color had been imparted to the fluid from the bacilli themselves, as could be shown by diluting a portion of it to the original bulk and comparing it to the bouillon before extraction. The filtered product had a peculiar odor, similar to but more pronounced than that of the culture itself before extraction, and suggesting the odor of beeswax. This substance was employed during most of our experiments under the name of "lepratoxine," although in the latter part of our work, when the glycerin contained in the extract was interfering with the progressive increase of our doses, we endeavored to further strengthen this extract, without increasing its glycerin contents, by grinding (like Koch did in the preparation of his T. O. and T. R. and later in his preparation of B. E.) the bodies of the bacilli in an agate mortar, without the addition of glass or other foreign substances. We found that this grinding process, if sufficient labor and patience was exercised, was completely successful in reducing the bacilli to a nonacid-fast granular mass. We added one-half per cent by weight of this ground material (dry) to the "lepratoxine" just described.

Inasmuch, however, as we could note very little difference in the effect produced by the filtered toxine and the filtered toxine reenforced by the ground extract, we have not separated these two substances in our description of the employment of the "lepratoxine" on our patients. If there was any difference between these two extracts, it was that the extract containing the ground-up organisms showed a greater tendency to produce local irritation at the site of injection.

By means of grinding and centrifuging repeatedly (after the method of Koch), we also prepared what corresponds to Koch's T. O. and T. R.; but inasmuch as the "lepratoxine" that had been reenforced with the ground bacilli contained all the elements that are met with in T. O. and T. R., we did not systematically employ the latter substances alone on our patient, chiefly because we were limited as to the number of patients that we could secure for treatment, so were forced to limit the number of modes of treatment.

IV. FATTY SUBSTANCES OF THE *B. lepræ* CULTURES.

After some preliminary experiments with various fat solvents, such as alcohol, alcohol and ether, ether, chloroform, chloroform and alcohol, xylol, sodium hydroxide, solution of soap in alcohol, and solution

of sodium hydroxide in absolute alcohol, we reached the conclusion that the greatest amount of yellowish-colored fatlike material could be extracted from our bacilli when a mixture of chloroform and alcohol was employed. No systematic attempt was made to identify this fatlike substance, or (what is more probable) mixture of fatty substances, except that we were able to show that a certain percentage of this material extracted with chloroform and alcohol was soluble in acetone and a certain percentage was insoluble in acetone. It was noted that bacilli that had been extracted with chloroform and alcohol lost some but not all of their acid-fastness. On the other hand the bacilli, after this treatment, seemed to be separated one from another and no longer occurred in bundles, and it was thought from this that possibly some fatty material that acted as a binding substance in holding together zooglœic masses had been extracted by this mixture—more than the fatty material within the body of the bacillus, that gives the latter its acid-fastness.

This fatty extract, when filtered and evaporated down to a solid mass, was of an orange-yellow color, could be stained with Ziehl-Nielson carbol-fuchsin, and held that stain against treatment by acid.

Considerable difficulty was experienced in getting this fatty material in a suspension capable of being used as an injection, and in doing this, for fear of causing emboli, we avoided employing any of the heavy oils as our vehicle. We found, however, that if this bacterial fat was freed from its chloroform and alcohol and ether added to it a *partial* solution of the substance occurred. To this ether solution a quantity of alcohol was added, the mixture shaken, and a quantity of water added. This made a fairly perfect suspension, which was not usually broken by the subsequent evaporating off of a large part of the ether. The final product, consisting of a menstruum of water and alcohol, containing a trace of ether, suspending the bacterial fat.

As will be seen from the above, this substance was prepared somewhat similar to Deycke's "nastin," but it presented, of course, decided differences, not only being from an entirely different organism, but in our experience ether was not a satisfactory extracting agent for *B. lepræ*, although it proved to be with Deycke's *Streptothrix leproides*. Nor did we, on account of the dangers just mentioned, care to imitate Deycke by using a heavy oil as our menstruum.

V. "SENSITIZED" KILLED CULTURES OF *B. Lepræ*.

We chose a large young *Macacus rhesus* monkey, and inoculated him heavily with the cultures of several of our "strains" of our *B. lepræ*. One month later we extracted 1 c. c. of the animal's heart blood during life by puncturing that organ with a hypodermic needle. We diluted this blood with equal volume of water and added the

mixture to one agar-slant culture of our organism (strain "H"). Instead of forming a suspension, as would have occurred had saline solution or water alone been used, this mixture of monkey blood and water, soon after its transfer to a test tube, caused clumping of the whole suspension of bacilli. To this test tube we added as "complement" 1 c. c. of guinea pig's blood and incubated the mixture for several hours. At the end of this time we found that the clumping still continued, but that no morphological changes had occurred in the individual bacilli. We then diluted freely with a definite quantity of saline solution and placed the mixture in the ice chest. After 48 hours the clumping action had ceased, and the bacilli could easily be shaken up into a perfectly homogeneous emulsion. We then heated this mixture to 60° C. for one hour to kill the lepra bacilli and to inactivate the animal's blood sera. In order to preserve this mixture, we added 1 per cent phenol and kept the flasks and their contents in the ice chest.

VI. SERUM OF A HORSE, WHICH ANIMAL HAD BEEN MORE OR LESS COMPLETELY IMMUNIZED AGAINST STRAINS B, F, G, AND H OF OUR CULTURES OF *B. lepræ*.

We chose a horse, weighing about 1,000 pounds, and injected, at short intervals, live cultures of our several strains of acid-fast bacilli, suspended in normal saline solution. The injections were given into the jugular vein by means of an ordinary large hypodermic syringe and every precaution taken against contamination of the material. We began with relatively small doses of our cultures, but increased the dose with each administration, until finally we gave 18 to 20 agar cultures of the bacilli at a dose. After these injections the animal became quite ill, and its temperature rose as high as 40° C. None of the injections, however, caused abscesses, possibly due to the fact that they were given directly into the general circulation.

After several months' treatment of this kind we bled the animal and found that its blood serum clumped *all* our cultures of *B. lepræ* in a dilution of 1:1000 and strongly clumped them in a dilution of 1 to 500. On the other hand, as a control, neither *B. margaritæ*, *B. smegmæ*, or the grass bacillus of Moeller was in any way affected by the action of the serum, not the slightest clumping occurring even when we used 1 part of serum to 50 parts of salt solution.

This clumping was not accompanied by *bacteriolytic* action, nor was such action brought about by supplying normal guinea pig serum to the mixture (on the possibility that it would serve as complement). The *bactericidal* properties of the serum have not at the present writing been thoroughly worked out, but the following experiment was tried:

A quantity of serum of a dilution of 1 to 40 was added to a mixture of cholera and leprosy bacilli (which mixture was growing well

together up to the time of treatment with serum); after exposure to the serum the *S. cholerae* grew readily, while *B. leprae* failed to show any growth when planted on glycerin agar.

It is only fair to state here that we did not consider it at all probable that this horse had been immunized long enough to possibly produce a curative serum, but when we secured this evidence of agglutinin production we felt justified in temporarily discontinuing the injection of the animal in order that we might obtain a quantity of its serum and employ it on our patients. After obtaining a quantity of this animal's serum for our purposes we again resumed our attempts to immunize it, and are still carrying on these injections of our horse in hopes of obtaining a more potent serum.

ANIMAL EXPERIMENTS WITH THE ABOVE-MENTIONED SUBSTANCES.

We injected ordinary laboratory animals with all of the above-mentioned substances in order to first ascertain whether they were free from pathogenic extraneous organisms, and also to note any physiological effect that these substances might produce. A number of animals were used in these tests, but for sake of brevity we will summarize the effects noted with each substance employed.

The vaccine caused the same local effect on rabbits, guinea pigs, and rats, namely, an area of coagulation necrosis at the site of injection, followed either by absorption or abscess formation, depending on the dose and strength of the vaccine given. There was no general effect appreciable.

The live cultures usually caused nodules at the site of injection, accompanied by about the same pathological changes as were noted when the killed cultures (vaccine) were given. It was thought that the animals receiving the live cultures showed more evidence of a general effect than when the vaccine was employed, but this was only in a general way, and most of the animals appeared unaffected by the injection. One guinea pig died, apparently as a result of placing a loopful of live cultures, recently isolated from a leper, under the animal's skin, and some of the other animals were made ill.

The "lepratoxine" that did not contain ground bacilli caused neither local nor general effects in the animals inoculated with it. The "lepratoxine" which contained ground bacilli produced a slight local reaction at the site of injection, but in the few experiments tried it did not cause abscesses, as the unground vaccine had.

The fatty extract, obtained by the use of chloroform and alcohol, when given in large doses, caused an abscess to form at the site of inoculation, without any appreciable general disturbances.

The "sensitized" killed cultures of the lepra bacilli caused neither general nor local effects, even when injected into the peritoneal cavity.

This absence of local effects may have been due to the fact that the suspension contained a much fewer number of organisms per cubic centimeter than our "vaccine" did.

The horse's serum was without any appreciable effect on the animals that received it.

THE USE OF THESE SUBSTANCES ON THE PATIENTS UNDER OUR CARE.

Owing to the fact that the number of our patients was limited, we had in most instances to employ one of the above substances for a time, and then, after abandoning its use, employ another one of our substances on the same patient. As none of the substances employed, however, have apparently been of much if any benefit to the patients receiving it, we do not consider this to be a serious flaw in the data that we have to present. Inasmuch, however, as a single patient received more than one substance, it will be convenient to give a history in tabular form of each of the patients treated, and in this table to include the data on the use of the substances which we are discussing.

Patient.	Sex.	Age.	Type of disease.	Duration.	Nature of product used.	Dose.	Number of injections.	Duration of treatment.	Local reaction.	General reaction.	Remarks.
16	Female...	18	Nodular leprosy.	1 year...	Vaccine.....	Initial, 20,000,000, increasing to 250,000,000.	7	35 days..	Following 3d, 4th, and 5th injection. Abscess following 6th and 7th injection.	Following the 5th injection.	Erythematous induration on the face almost entirely absorbed. Macular eruptions disappeared from the trunk. Many nodules on the extremities were absorbed, leaving pigmented areas. Lesions in the nose became healed.
17	Male....	18	Nodular leprosy.	1 year...	Vaccine.....	Initial, 5,000,000, increasing to 375,000,000.	23	121 days.	Following the 12th, 13th, 17th, 19th, 22d, and 23d injections.	Following the 17th, 21st, 22d and 23d injections.	Hypæremia increased on buttocks, ulceration of the septum healed. Acid-fast bacilli disappeared from the nose.
18	Male....	18	Nodular leprosy.	3 years..	Vaccine.....	Initial, 2,500,000, increasing to 250,000,000.	9	42 days..	Following the 2d, 3d, 4th, and 5th injections.	Following the 17th, 18th, 21st, 22d, 23d, and 24th.	
					Lepratoxine.	Initial, 0.06 c. c., increasing to 2 c. c.	24	121 days.	Abscess following the 6th, 7th, 8th, and 9th. All caused local reactions except 4th, 5th, 7th, 9th, and 10th, 20th and 21st causing abscess.	Fifth injection caused a marked general reaction.	There is less infiltration of the skin of the face, and the nodules are softer.
19	Male....	15	Macular leprosy.	2½ years.	Vaccine.....	Initial, 5,000,000 to 375,000,000.	17	100 days.	Following the 12th (abscess), 13th (abscess), 14th, 15th, 16th, and 17th (abscess) injections.	Following the 14th and 17th injections.	
					Live culture vaccine.	6,000,000, 10,000,000, and 20,000,000.	3	62 days..	Following the first injection.		No improvement.
					Vaccine.....	Initial, 5,000,000 to 375,000,000.	9	49 days..	Following the 4th, 5th, 6th (abscess), 7th (abscess), 8th (abscess), and 9th (abscess).		
					Live culture vaccine.	250,000.....	1	7 days..			

Patient	Sex.	Age.	Type of disease.	Duration.	Nature of product used.	Dose.	Number of injections.	Duration of treatment.	Local reaction.	General reaction.	Remarks.
					Lepratoxine.	Initial, 0.04 c. c. to 2 c. c.	25	163 days.	Following the 4th, 5th, 7th, 14th (abscess), 17th, 18th, 19th, 20th (abscess), 22d (abscess), 24th, and 25th injections.	Following the 5th, 12th, 16th, 18th, 23d, and 24th injections.	
20	Female..	12	Nodular leprosy.	4 years...	Lepratoxine.	Initial, 0.01 c. c. to 2 c. c.	16	261 days.	Following the 2d, 3d (abscess), 4th, 8th, 11th, 12th (abscess), 13th (abscess), and 15th injections.	Following the 4th, 5th, 7th, 8th, remittent temperature for 55 days, with an eruption, in successive crops of papules and nodules, 9th, 10th, 14th, and 15th injections.	A considerable decrease in the infiltration of the face and the ears.
21	Female..	27	Nodular leprosy.	3 years..	Lepratoxine.	Initial, 0.02 c. c., increasing to 5 c. c.	16	253 days.	Following the 3d, 4th, 9th, 11th, and 12th (abscess), 13th, 15th, and 16th injections.	Following the 3d, 10th (remittent or intermittent temperature, in successive crops of papules and nodules for 77 days, many old nodules entirely absorbed during this period), 12th, 13th, 15th, and 16th injections.	No improvement.
22	Female..	19	Nodular leprosy.	5 years..	Lepratoxine.	Initial, 0.04 c. c., increasing to 2 c. c.	32	260 days.	Following the 3d, 4th, 10th, 12th, 18th, 19th, and all injections from 22d to 30th, inclusive; 31st injection (abscess).	Following the 4th injection.	The nodules on the forehead were partially absorbed.
23	Male....	17	Macular leprosy.	3 months	Vaccine.....	50,000,000.....	1	7 days...			Hyperemia and infiltration of the face increased.
					Lepratoxine.	Initial, 0.04 c. c., increasing to 2 c. c.	14	59 days..	Following the 14th injection.	Following the 4th (frontal headache) and 12th injections.	
					Live culture vaccine.....		10	133 days.			
					1st injection, 1/3 osce. 2d injection, 1/3 osce. 3d injection, 2/5 osce.						

24	Female..	14	Macular leprosy.	9 months	4th injection, 1 oese. 5th injection, 2 oesen. 6th injection, 5 oesen. 7th injection, 8 oesen. 8th injection, 1 oese. 9th injection, 2 oesen. 10th injection, 3 oesen.	1	7 days..			Marked improvement in leprosy lesions.
			Vaccine.....		500,000,000.....					
			Lepratoxine.		Initial, 0.04 c. c., increasing to 1 c. c.	11	100 days.	Following the 1st, 2d, 6th, and 11th injections.	Following the 6th and 11th injections.	
24	Female..	27	Nodular leprosy.	2 years..	Initial, 20 c. c.; 10 days later, 45 c. c.; 34 days later, 35 c. c.; 14 days later, 45 c. c.; 21 days later, 40 c. c.	5	89 days..	Following the 3d and 5th injection urticaria.	Following the 1st injection (chest pains and cough), 2d, 3d, and 4th injections (general muscular pains), 5th injection pains in left arm, neuralgic in character.	No improvement noted. Subjectively, patient claimed infiltration around eyelids has decreased, permitting her to more easily open her eyelids.
40	Male....	40	Nodular leprosy.	5 years..	Initial, 45 c. c.; 21 days later, 40 c. c.	2	21 days..			Patient is still under same treatment and observation.
27	Male...	42	Anæsthetic leprosy.	7 years..	Initial, 1 c. c., increasing to 3 c. c.	5	44 days..	Following the 2d and 3d injections.	Following all the injections.	No change noticed.
36	Male....	36	Nodular leprosy.	1½ years.	1 c. c.....	2	10 days..		Following the 2d injection.	Treatment discontinued by request of patient.
			Acid-fast fatty substance of <i>B. Lepræ</i> .							

SUMMARY AND DISCUSSION.

It will be seen from the above that we have prepared and tried, more or less thoroughly, a number of substances, prepared directly or indirectly from our cultures of *B. lepræ*. Our efforts along this line appear to us to have been sufficient to permit us to form some opinion as to the possible utility of such therapeutic means, and from the data we have it appears to us that the following may be stated:

First. That vaccine (ordinary, suspended killed cultures of *B. lepræ*) can not be advantageously employed in the treatment of leprosy unless very small doses are used, owing to the slow absorption of the material and its tendency to cause abscesses.

Second. Live cultures of *B. lepræ*, while they have produced no beneficial results in our hands, are deserving of further trial. Small doses should be used to avoid abscess formation.

Third. Toxines prepared from *B. lepræ* after the method of Koch's "old tuberculin" and his "B. E.," appear to be of little or no value, in our experience, in the treatment of leprosy.

Fourth. The extract, consisting of fatty material, obtained from lepra bacilli has not been employed for a sufficient length of time to determine whether it is of value in the treatment of leprosy.

Fifth. The serum of a horse, which animal had received injections of lepra bacilli, has been without any beneficial results to patients suffering from leprosy during the short period we have used it; but from the fact that this animal's serum strongly agglutinates *B. lepræ* cultures, we are not without hopes of increasing the potency of this serum to a point where it may be of benefit in the treatment of this disease.

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LIST OF PUBLIC HEALTH BULLETINS.

The following is a list of the Public Health Bulletins that have been issued:

- *1. Report on Trichinæ and Trichinosis. By W. C. W. Glazier. 1881. 212 pages. 87 il. 1 map. Paper. Senate Executive Document No 9, Forty-sixth Congress, third session. Out of print.
- *2. Report on the Etiology and Prevention of Yellow Fever. By George M Sternberg. 1890. 271 pages. 21 pl. 20 il. Cloth. Out of print.
- *3. Mortality Statistics in the United States for the year ending December 31, 1897. From Annual Report Marine-Hospital Service, 1898. 24 pages. Paper. Out of print.
4. Yellow Fever: Its Nature, Diagnosis, Treatment, and Prophylaxis and Quarantine Regulations Relating thereto. By officers of the Marine-Hospital Service. Reprint from Annual Report Marine-Hospital Service, 1898. 176 pages. 1 il. Paper.
- *5. Shipment of Merchandise from a Town infected with Yellow Fever. By H. R. Carter. 1899. 15 pages. Paper. Out of print.
6. Report of Commission of Medical Officers detailed by authority of the President to Investigate the Cause of Yellow Fever. By Eugene Wasdin and H. D. Geddings. July, 1899. 98 pages. 26 charts 2 il. Paper.
- *7. The Bubonic Plague. By Walter Wyman. January, 1900. 50 pages. Paper. Superintendent of Documents, 5 cents.
- *8. Report of Commission appointed by the Secretary of the Treasury for the Investigation of Plague in San Francisco. By Prof. Simon Flexner, Prof. F. G. Novy, and Prof. L. F. Barker. January 23, 1901. 23 pages. 1 map. Paper. Out of print.
- *9. Report Relating to the Origin and Prevalence of Leprosy in the United States By a Commission of Medical Officers of the U. S. Marine-Hospital Service. 1902. 119 pages. 25 il. Paper. Senate Document No. 269, Fifty-seventh Congress, first session. Superintendent of Documents. Cloth, \$1.00
- *10. Plague Conference. Containing a copy of the address of the chairman, and resolutions passed by a conference called in accordance with requests from a number of State Boards of Health, and under authority of section 7, act of Congress approved July 1, 1902, to consider the plague situation. Reprint from P. H. R. No. 4, Vol. XVIII, January 23, 1903. 9 pages. And February 6, 1903. 41 pages. Paper. Out of print.
- *11. Transactions of the First Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. June, 1903. 120 pages. Cloth. Out of Print.
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13. The Public Health and Marine-Hospital Service of the United States. A Brief History. Prepared for the Louisiana Purchase Exposition. December, 1904. 16 pages. Paper.
- *14. Sanatorium for Consumptives, Fort Stanton, N. Mex. By P. M. Carrington. Reprint from Annual Report Public Health and Marine-Hospital Service, 1904. 19 pages. Paper. Out of print.

15. Transactions of the Third Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. May, 1905. 52 pages. Cloth.
16. How to Prevent Yellow Fever—No Mosquitoes, No Yellow Fever. By Walter Wyman. July 31, 1905. 3 pages. Circular.
17. Transactions of the Fourth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. May, 1906. 75 pages. Cloth.
18. Transactions of the Fifth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. May, 1907. 47 pages. Cloth.
19. Trachoma, Its Character and Effects. By Taliaferro Clark, and J. W. Scherschewsky. 1907. 34 pages. 6 il. Paper
- *20. The Public Health and Marine-Hospital Service of the United States. A Brief History. Prepared for the Jamestown Ter-Centennial Exposition. 1907. 12 pages. Paper. Out of print.
- *21. Transactions of the Sixth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. April, 1908. 79 pages. Cloth. Out of print.
- *22. The Present Pandemic of Plague. By J. M. Eager. 1908. 30 pages. Paper. Out of print.
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- *25. Hookworm Disease. Reprint from Annual Report P. H. and M. H. S., 1908. 5 pages. Paper. Out of print.
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 7. Ecto Parasites of the Rat. By N. Banks.
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 9. Rodents in Relation to the Transmission of Bubonic Plague. By Rupert Blue.
 10. Rodent Extermination. Rats and Mice. By W. C. Rucker.
 11. Natural Enemies of Rats. By D. E. Lantz.
 12. Rat-Proofing as an Anti plague Measure. By R. H. Creel.
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 15. The Rat in Relation to Shipping. By W. C. Hobdy.
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- *31. Transactions of the Seventh Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. June, 1909. 86 pages. Cloth. Exhausted.
32. Hookworm Disease (or Ground-Itch Anemia), its Nature, Treatment, and Prevention. By Prof. C. W. Stiles. 1910. 40 pages. Paper.
 33. Studies upon Leprosy. 1910. 25 pages. Paper.
 - VII. A Statistical Study of an Endemic Focus of Leprosy. By W. R. Brinckerhoff and A. C. Reinecke.
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 37. The Sanitary Privy: Its Purpose and Construction. By Prof. C. W. Stiles. 1910. 24 pages. 12 figs. Paper.
 38. General Observations on the Bionomics of the Rodent and Human Fleas. By M. B. Mitzmain. 1910. 34 pages. Paper.
 39. Studies upon Leprosy. September, 1910. 50 pages. Paper.
 - IX. Mosquitoes in Relation to the Transmission of Leprosy.
 - X. Flies in Relation to the Transmission of Leprosy. By D. H. Currie.
 - XI. Heredity Versus Environment in Leprosy. By H. T. Hollmann.
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41. Studies upon Leprosy. November, 1910. 36 pages. Paper.
 - XII. Notes on the Study of Histories of Lepers from the Standpoint of Transmission. By D. H. Currie.
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42. Disinfectants: Their Use and Application in the Prevention of Communicable Diseases. By T. B. McClintic. December, 1910. 46 pages. Paper.
 43. Experimental Studies of Plague and a Plague-like Disease among Rodents. By George W. McCoy. April, 1911. 71 pages. 7 pls. Paper.
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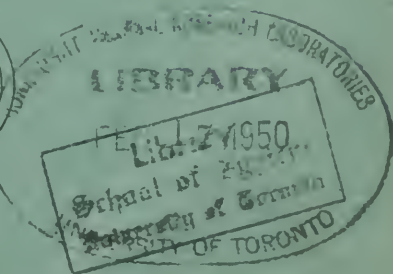
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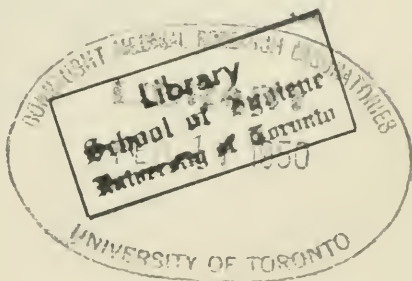
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PREFACE.

The second edition of this bulletin is prepared to meet a demand for a brief general account of a disease which, at the time the first edition was issued, was practically unknown to most of the American medical profession, and which probably still remains almost unknown to many of them.

Long stated to be nonexistent in the United States, pellagra was recognized but a short time ago, with almost startling suddenness, as being not only existent, but quite prevalent in various localities of this country. In the short space of the four or five years since intervening, this disease has assumed a position of great importance in the attention of both the medical and lay worlds.

While the malady is still largely confined to certain sections of the United States, it has shown itself to be a respecter of neither locality nor person, and may now be met with anywhere in this country. It deserves the careful consideration of every American medical man.

The kind reception accorded the first edition of this bulletin leads the writer to hope that this edition may also prove of some value to those who seek information regarding this important disease.

My indebtedness to the general literature of pellagra is evident, and, in addition to the references given, I desire to make here a general acknowledgment. I take pleasure also in expressing my thanks to my friend, Dr. J. W. Babcock, for helpful suggestions in the preparation of this bulletin, as well as for many other courtesies.



SOUTH CAROLINA CASE. NOTE THE DARK COLOR OF THE ERYTHEMA, AND THE LINE OF DEMARCATION.

Courtesy of Dr. J. J. Watson, Columbia, S. C.

PELLAGRA.

(Maïdismus, psychoneurosis maïdica, and a variety of other names.)

HISTORICAL.

There is naturally some uncertainty as to just when pellagra¹ was discovered, but this disease seems to have been first recognized among the peasantry of northern Spain, and the credit for its first description (1735) is almost unanimously given to Gaspar Casal, of Oviedo, a small town in the Asturias. From its characteristic erythema it was called *mal de la rosa*, and was regarded by Casal as "a peculiar kind of disease consisting of a combination of scurvy and leprosy."

About 20 years after Casal's observations a distinguished physician of the Venetian States, Antonio Pujati, independently described a similar disease in the district of Feltre in northern Italy under the name Alpine scurvy. In 1771 F. Frapolli, of Milan, published an account of a similar disease, to which he applied the popular name *pelagra* (with one l). Publications now followed by Zanetti, Odoardi, Gherardini, and others. In 1784, by order of Joseph II of Austria, the first *pellagrosario*, or hospital for pellagrins, was established at Legnano, and Gaetano Strambio was placed in charge. From there he published many of his well-known studies of the disease.

Through the publications of F. Fanzago (1789) the identity of Alpine scurvy and *pelagra* began to make itself manifest, and later, through Roussel's observations, *mal de la rosa* was shown to be the same affection.

By the beginning of the nineteenth century the disease was widely known all over northern Italy. It had apparently spread rapidly, showed a marked intensity, and was accompanied by a high mortality. From then till now pellagra has attracted much attention in Italy, and numerous authors have made notable contributions to the disease. Lombroso's work should be especially mentioned.

In France the disease was first observed early in the nineteenth century by the elder Hameau in the vicinity of Teste-de-Buch, whence the name, *maladie de la Teste*. Many French authors have made

¹ The etymology of the word is usually given: Italian, *pelle*, skin, and *agra*, rough. The name pellagra was first adopted by Frapolli, who already found it in use among the people. He spelled it "pelagra," and it is still seen so written, at times, in Spanish literature.

contributions to the disease, notably Théophile Roussel, whose most important work was published in 1866.

The disease later was reported in Roumania by Théodori (1858), in Egypt by Pruner (1847), and from other parts of southern Europe and the Mediterranean littoral by various observers.

The United States apparently for many years remained singularly free of this malady. The general consensus of opinion among medical writers had always been that pellagra did not occur in this country, and among the American medical profession its features were, up to a short time ago, almost universally unknown.

Sporadic cases were reported by Gray, of New York, and Tyler, of Massachusetts, as early as 1864. Sherwell, of Brooklyn, N. Y., reported a case in an Italian sailor in 1883, and also another case in 1902. Bemis is reported to have diagnosed a case in New Orleans in 1889, and a case is said to have occurred in North Carolina the same year (Wood and Bellamy). Harris, of Atlanta, reported a case in 1902. An epidemic of the disease occurred at the Mount Vernon (Ala.) Asylum for Negroes in 1906. These cases were studied by Searcy, McCafferty, Bondurant, and Dyer, and the outbreak was reported by Searcy in 1907. During the same year the diagnosis of pellagra was independently made by Babcock at the State Insane Asylum, Columbia, S. C., and a careful report made regarding the matter. Shortly after this Wood and Bellamy, of Wilmington, N. C., reported cases. The American disease was identified with Italian pellagra in 1908 independently by Watson and Babcock. In the spring and summer of this year pellagra began to be recognized quite generally through the southern United States.

Reports of the disease were made by the writer from Wilmington, N. C., to the Surgeon General of the Public Health and Marine Hospital Service in 1908; and in the succeeding months of this and the following years much interest was manifested in this disease by various municipal, county, and State medical organizations. In addition, two large conferences were held at Columbia, S. C., under the auspices of the South Carolina State Board of Health, and a national organization was formed for the study of the disease (November, 1909). During this same period several outbreaks of the disease were recorded in various parts of the country, especially in insane asylums, and the malady was found existent in some of the Northern States, notably Illinois and, later, Pennsylvania.

This, in a general way, gives a brief outline of the recognition and progress of this disease in the United States. An analysis of these various reports and a careful study of the development of pellagra in this country give good reason for the belief that the disease has, in all probability, existed in this country for many years; just how many it is difficult to say, perhaps 40 or 50, possibly longer. It does

not seem likely, however, that the disease had existed to any great extent; on the contrary, it seems far more probable that in all likelihood it was sporadic. Certainly it is hardly credible that it could have existed unrecognized in anything like the number of cases found in 1907 and subsequent years.

The recognition and development of pellagra in the United States bears a marked similarity to the history of the recognition and development of this disease in northern Italy in the eighteenth century. In both countries pellagra seemed to appear with almost startling suddenness, apparently spread with great rapidity, and was characterized by a marked intensity and a high mortality.

GEOGRAPHICAL DISTRIBUTION AND STATISTICS.

In 1866 Roussel¹ wrote:

Recently this malady has invaded new countries, and to-day it is found to the south of 47° of north latitude, between 10° of longitude west and even beyond 25° of longitude east, meridian of Paris, extending over a long zone of the temperate region of Europe from Cape Finisterre to the banks of the Sereth, across the Pyrenees Provinces of Spain and of France, upper and central Italy, and, in the basin of the Danube, upon the eastern and southern slopes of the Carpathians even to the frontiers of the Russian Empire.

Within the last half century, however, pellagra has been found more extensive than this and is now known to be endemic in various parts of both the Eastern and Western Hemispheres.

It is highly probable that the real geographic distribution of pellagra is unknown, but the disease has been reported from parts of Italy, Roumania, Austria-Hungary, Spain, France, and other places in southern Europe; from Asia Minor, India, and the Philippine Islands; also from Lower Egypt and some other places in North as well as South Africa. It is said to occur in New Caledonia, and sporadically in parts of South America, and possibly in Central America. It is also found in the West Indies, Mexico, and the United States.

At the present time it is most prevalent in northern and central Italy, certain parts of Roumania, and Austria-Hungary, and the United States.

It is thus seen that pellagra is rather widely spread, and occurs quite generally within the Tropical and the warmer parts of the Temperate Zones. A more detailed study, however, will show that while thus widely spread its local geographic distribution often displays many peculiar and striking limitations. The disease has been, and still is, a veritable scourge to certain parts of Europe, and it seems not unlikely that the United States may also have a similar experience. Without attempting to give full data, some idea of its extent may be gained by quoting certain statistics.

¹ *Traité de la pellagre et des pseudo-pellagres*, Paris, 1866.

According to official statistics, Italy had, in 1879, nearly 100,000 pellagrins; the number increased by 1881 to nearly 105,000. Since then there has been a steady decline, and at the present time there are said to be less than 50,000 cases in the entire kingdom. Up to recent years there have been from 2,500 to 4,000 deaths annually in Italy from pellagra, but of late this number has been greatly reduced and in 1908 fell to less than 1,500. In some restricted localities of Italy the percentage of the population suffering from pellagra is very high. But in considering comparatively large areas, in those places where the disease is most prevalent, the percentage of the total population stricken will run from 1 to 3, rarely 5 per cent. It has been stated that in Italy from 4 to 10 per cent of pellagrins suffer from serious mental disorder. The disease is almost entirely confined to northern and central Italy, but seems of late to be slowly spreading southward.

In certain parts of Austria the disease is quite prevalent; and recently it is reported that among a population of 2,250,000 investigated there were found 78,163 pellagrins (3 per cent). In Roumania there were reported to be, in 1906, over 100,000 cases of the disease. It is largely confined to southern Roumania, but in recent years seems slowly advancing northward. The disease is also very prevalent in Lower Egypt.

In the United States statistical data are lacking. The disease is not required to be reported except in four States, and in only one are such reports required by law. It is difficult even to make an estimate of how many cases there may be. It has been reported quite generally, but its chief area seems to be in the Southeastern States—in a general way those which lie south of the Potomac and Ohio and east of the Mississippi Rivers, with Louisiana and Texas included. The malady is undoubtedly increasing in numbers and spreading into new territory. There are certainly many thousand cases of the disease in this country, and the present situation must be looked upon with grave concern. A recent editorial writer¹ has said: "This is one of the most, if not the most, important public health problem of the present."

ETIOLOGY.

While the etiology of pellagra is obscure, the disease has nevertheless almost unanimously been regarded as a food poisoning, allied to ergotism or beriberi, and attributed to the use of Indian corn² as an article of diet.

The idea of some causal relation of this kind between corn and pellagra seems to have originated with Casal, who first described the disease; but probably also was independently suggested by other

¹ Journal American Medical Association, LVII, 10, Sept. 2, 1911.

² In this bulletin the words corn, Indian corn, and maize are used interchangeably.

early observers. Such a thought was founded apparently to some extent on an historical basis. Medical men having found a new disease of rather striking characteristics, sought some new, recently acting cause to account for it. For certain reasons their attention was directed to Indian corn. The introduction and subsequent cultivation and use of this grain as food was thought to have been of comparatively recent occurrence in Europe, and pellagra was believed to have followed in its wake.¹

In whatever way it may have occurred, the corn theory of pellagra in some form originated almost simultaneously with the discovery of the disease, and from then till now has held a dominant place in the consideration of its etiology.

This idea was for a long while entertained in a loose, vague sort of way. It was probably first formulated (about 1810) by Marzari, who thus created what is called the *zeist* (from *Zea mays*) school. Marzari's idea that corn caused pellagra by its deficiency in certain nutritive principles was soon supplanted by Balardini, who first introduced the view that the disease was due to a certain mold sometimes found on the grain. The greenish color of the mold gave the name *verdet* to this theory. Balardini was thus the creator or inspirer of the idea that pellagra is due, not to the use of good corn, but to the use of damaged or fermented grain.² Later Lombroso, actuated largely by philanthropic motives, devoted many years of his life to the development and defense of this theory of the cause of pellagra.

As is to be expected, in a disease of obscure etiology, theories are numerous. It has long been customary to divide all theories of pellagra into two general classes: The *zeists*, or those who hold the view that there is some causal relation between corn and pellagra, and the *antizeists*, who oppose this view.

In support of their theories the *zeists* make the following general statements:

(1) The disease appeared for the first time in Europe after the introduction of maize, probably from America, and followed everywhere the extension of the cultivation of this new grain and its adoption as an article of food.

(2) Pellagra is found endemic only in countries where maize is extensively used as an article of diet.

(3) Pellagra diminishes or disappears, among individuals or groups of individuals, whenever maize is eliminated from their diet-

¹ In the history of the introduction and subsequent cultivation of corn in Europe there are many obscure points, concerning which no opinion is here expressed.

² Throughout this bulletin the words "spoiled," "damaged," or "fermented," as applied to corn, are used interchangeably to express a deterioration of the grain accompanied by the development of various parasites (bacteria and molds) thereon. This deterioration is doubtless a complex process and not always uniform. Under certain conditions it may also occur in food prepared from corn.

ary. On the other hand, it is likely to appear among people who adopt this cereal as a large part of their food supply.

Sharing the general opinion of some etiological relation between corn and pellagra, the zeists, however, hold many different opinions as to the exact nature of this relation. Their principal views may be briefly stated thus:

1. The idea that maize as a foodstuff is wanting in proper nutritive value. This conception is in reality no longer held, having been rather effectually discredited by many careful analyses of maize, which show that this cereal possesses high nutritive value, is rich in fats and nitrogenous substances, and is easily assimilable. Pellagra is, moreover, not infrequently found among well-nourished individuals, and its symptomatology is not that of inanition. It is, however, worthy of comment that in the writer's experience the average Italian practitioner, especially in the country districts, seems to regard spoiled corn only as a predisposing cause and the disease apparently as a nutritional disturbance. Studies on the metabolism of pellagrins have yielded some interesting results, but so far have shed little light upon etiology.

2. The idea that good, sound maize contains certain toxic substances which cause pellagra. This is another view which has been largely discredited by the absence of pellagra in so many places where maize is, and has been for long periods, extensively used as food.

3. The toxico-chemical idea that under the influence of saprophytes (bacteria or molds) maize may undergo certain changes with the formation of one or more toxic substances of a chemical nature (exogenous poisons). This is the great spoiled-corn theory that "in pellagra we are dealing with an intoxication produced by poisons developed in spoiled corn through the action of certain microorganisms, in themselves harmless to man." This idea has a host of adherents. It was established through the admirable labors of Lombroso, who has been its great advocate and exponent, and is perhaps to-day the most popular of all the various phases of the maize theory. This is the view accepted by the Italian Government in its extensive prophylactic measures. It is not without critics and antagonists, however, and Lombroso's experimental work and conclusions have been seriously called in question by many able students of the disease.

Lombroso¹ failed directly to incriminate any particular micro-organism. Investigating chemically the poisons involved, he described three substances, a red oil, a highly toxic substance, or pellagrosine, and a resinous substance. Pellagrosine he found the most toxic of all. It is probably not a pure substance and may contain more than one active principle. Experimenting with these sub-

¹Trattato profilattico e clinico della pellagra, Turin, 1892.

stances on man and certain lower animals, he observed phenomena allied to pellagrous symptoms, but it is a fairly general opinion that such phenomena are not comparable to pellagra in man.

A great many students have accepted Lombroso's ideas in a general way, and followed him in this field, seeking principally to determine the character of the toxic substances produced and the micro-organisms responsible for them. Many toxic substances have been obtained from spoiled maize, and a rich flora has been described occurring on the damaged grain, but no evidence has yet been submitted which can be accepted as conclusive.

It may be of interest to state that Babes¹ and other workers claim to have shown that there exists in the blood of pellagrins a substance which is antagonistic to the toxic action of extracts made from spoiled maize (antibodies).

Evidence of quite contrary character has, however, been brought forward by Raubitschek and others.²

4. The toxico-infective idea that from spoiled maize there is formed within the body certain toxic substances (endogenous). Neusser³ advocated the view that under some circumstances there is formed in maize, largely under the influence of the *Bacterium maydis*, a certain "receptive mother substance" which later, in the body, underwent a further change. Under other circumstances, however, he viewed the disease as a direct intoxication.

De Giaksa⁴ attributed great importance to the action of the colon bacillus on ingested maize. His idea seems to have been that the vegetating properties of this bacillus may become greatly modified on a culture medium of maize, and he alleges that he has shown the production, by the colon bacillus on maize media, of specific toxic substances.

Many similar views that the disease is an autointoxication of some kind have been entertained by various writers.

5. The idea that pellagra is a specific infection, derived from maize, either a mold or a bacterium.

The flora of maize has been frequently studied, and a great number of parasites named and described. Most of these, however, have attracted little attention with the exception of the fact that all may cause changes in the grain upon which they vegetate. *Penicillium glaucum*, the ordinary blue mold, has perhaps of late attracted most attention.

Pari incriminated the maize smut (*Ustilago maydis*), Majocchi and Cuboni attributed great importance to the *Bacterium maydis*, and Carrarioli described a *Bacillus pellagræ*.

¹ Pellagra, In Nothnagel's *Specielle Pathologie und Therapie*, XXIV, 1901.

² See Public Health Reports, Public Health and Marine-Hospital Service, XXVI, 8, Feb. 24, 1911.

³ *Wein. med. Presse*, 4, 146, 1887.

⁴ *Annali d'Igiene Sper.*, Roma, 1892 and 1903.

In 1902 Ceni¹ declared pellagra to be due to an infection by two molds, *Aspergillus fumigatus* and *flavescens*—a true aspergillosis. In a series of highly interesting papers he defended this view with great skill, but his work has not been confirmed. This infection he thought usually, but not necessarily, derived from spoiled corn.

In 1906 Tizzoni² began a series of publications advocating a specific bacterium which he called *Streptobacillus pellagræ*. This microorganism he found both in spoiled corn and in the blood, spinal fluid, and certain tissues of pellagrins. He has done a great deal of interesting work, but his results are also without confirmation.

Öospora verticilloides, *diploidia*, and other molds and bacteria found on spoiled maize have all received a share of attention.

(6) Quite recently Raubitschek³ and other writers have brought forward a photodynamic view of pellagra and sustained the opinion that all corn contains some toxic substance which, circulating in the blood stream, does not display its deleterious action until sensitized by the chemical rays of sunlight falling on exposed body surfaces. Attention is directed to the analogy with fagopyrismus seen in certain animals fed on buckwheat; and various experiments on animals, as well as other data, are quoted to support their idea.

The antizeists have always been greatly in the minority, but under the more or less recent stimulation of certain new ideas their side of the question has created widespread interest.

There have always been two general arguments against the maize theory:

(1) The extensive territory over which corn is and has been cultivated and used as food for many generations without the appearance of pellagra.

(2) The numerous cases of pellagra which may be found among individuals who do not use corn in their dietary.

To these of late have been added:

(3) Certain epidemiologic data, especially the peculiar topographical distribution of the disease, even in marked endemic centers. These reported observations do not readily lend themselves to the theory of a food poison from maize.

The antizeist schools may be classed as follows:

(1) The idea that pellagra is not a morbid entity has for a long while been entertained by a group of writers in France. They regard it as a morbus miseriæ and deem it a symptom complex which may arise in many cachectic states and especially in alcoholics and insane persons. They usually speak of it as the pellagrous syndrome. It was in the controversy with this school of thought that there was

¹ Rivista Sper. di Frenlat., etc., 1902.

² Estratto del Bollettino del Minist. di Agricolt., Indust. e Comm., Rome, 1909.

³ Public Health Reports, loco citato.

born the term pseudo-pellagra, which will be found mentioned elsewhere.

This idea has never been very broadly accepted. It is difficult to understand how doubt can arise that pellagra is a disease *sui generis* when consideration is given to its consistent symptomatology and morbid anatomy and its unique epidemiology.

(2) The idea that pellagra is a parasitic disease transmitted by a blood-sucking insect. This is the simulium theory of Sambon, first suggested by him in 1905, and later much amplified.¹ Sambon has not expressed any definite opinion as to the nature of the parasite, but thinks it may possibly be a protozoal organism. The transmitting agent, however, he thinks he has shown to be some one or more species of simulium or buffalo gnat.

This theory is based by Sambon upon the analogy of pellagra with certain other insect-borne, parasitic diseases, upon important epidemiologic studies made by him in Italy, and upon the agreement existing between certain phenomena peculiar to pellagra and the distribution, characteristics, and life history of the *Simuliidae*. In his work he has most thoroughly emphasized the peculiar topographical distribution of pellagra and its connection with the running stream in which the simulium breeds. This peculiar local distribution of the disease, in his opinion, can not be brought into harmony with any theory of a food poisoning.

His very interesting epidemiologic studies have marked a new and important departure in etiologic researches upon pellagra. The conception is a brilliant one. It has attracted wide attention and has stimulated everywhere renewed interest in the study of pellagra. It must, however, still be regarded as a theory until further work is done. Evidence is accumulating that American and Italian pellagra may show, on their epidemiologic side, many important differences. Studies in other countries may show even further variations.

(3) The idea that pellagra is a parasitic disease, caused by a water-borne, nematode worm. This is the hypothesis of Alessandrini, first brought out by him in 1910.²

His argument is very similar to Sambon's and rests upon the analogy between pellagra and some other diseases due to nematode worms, as well as upon epidemiologic studies made by him in Italy.

Both note the importance of the peculiar local distribution of the disease, and both connect it with water; but Alessandrini connects the disease with potable waters, and he claims to have found constantly in the shallow wells and small, slowly flowing streams of pellagrous regions numerous larvæ of the family *Filaridae*. They were rare or absent in the better potable waters found in regions where

¹ Progress Report on the Investigation of Pellagra. Journal of Tropical Medicine and Hygiene, XIII, 18, 19, 20, and 21, 1910.

² Sulla pellagra in Italia. Annali d' Ig. Sper., n. s., Vol. XX, fasc. IV, 1910.

pellagra did not occur. He also claims to have found certain very small ova in the little vesicles of the erythematous skin of pellagrins. To these he attributes possible importance.

(4) The idea that pellagra is a form of amebiasis. Siler and Nichols¹ first drew attention to the frequency of amebiasis in pellagrins. Long² later advocated a modified autointoxication idea of the cause of the disease, with the ameba as a large factor in the process. Young³ suggested that there might exist some hitherto undescribed species of ameba which would prove to be the specific cause.

It has often been observed that amebiasis is not infrequent in pellagrins, but apparently slight attention has been given to any discrimination between pathogenic and nonpathogenic forms. This would seem a point of essential importance.

The striking intestinal phenomena of pellagra almost inevitably suggest that here perhaps may be found the etiologic factor, but so far studies on the intestinal flora and fauna of pellagrins have not yielded any striking results.

Among the host of suggestions which have come to light on this matter, a recent one may be noted. Not so much for its scientific value, but more especially for the reasons that it incriminates what is regarded as a wholesome article of food in general use, and adds another to the many fears from which the laity already suffer with regard to this disease.

This suggestion attributes pellagra to the use of cotton-seed and other semidrying oils as articles of diet. By interweaving certain known chemical reactions with certain unsupported personal opinions, and then applying unwarranted inferences to the metabolism of the human body, it has been made to appear possible that some of the end oxidation products of these oils may cause the disease.

To the writer such a suggestion does not seem in harmony with many of the well-known facts of pellagra, and does not appear in accord with either its history, its epidemiology, or its clinical and pathological phenomena.

In the present state of this question the publication of immature speculations of this character, especially when they tend to arouse unjustifiable fears in the mind of the public, is strongly to be deprecated.

The above is but a brief summary of the many theories which have been put forward to account for this obscure disease.

From a careful review of the subject it would certainly seem safe to assert that in any definite, scientific sense, the cause of pellagra is unknown.

¹ Aspects of the pellagra problem in Illinois. National Conference on Pellagra, 1909.

² Pellagra. *Journal American Medical Association*, LV, 9, 1910.

³ Amœbæ as the cause of pellagra. *Jour. S. C. Med. Assn.*, VI, 11, 1910.





ILLINOIS CASE.—ERYTHEMA, SHOWING DESQUAMATION AND SUPERFICIAL
ULCERATIONS.

Courtesy of Dr. George A. Zeller, Superintendent Peoria State Hospital, Peoria, Ill.



SOUTH CAROLINA CASE.—THE WET TYPE OF ERYTHEMA.

From South Carolina State Board of Health Bulletin, December, 1910. Courtesy of South Carolina
State Board of Health.

Further, the idea of some etiological relation between maize and pellagra has long been accepted by the medical world, and is approved by the mature judgment and long labors of many experienced and able men. It is not, indeed, an established doctrine, but it is not in consonance with that conservatism which has usually characterized the medical profession totally to reject an accepted hypothesis unless it can be replaced by something much more tangible. It would be equally unwise to assume an attitude of dogmatic adherence to such a theory.

The theories of Sambon and Alessandrini mark a new and important departure in this field, and deserve the most careful consideration. For the present, at least, the various other ideas suggested do not promise much of consequence.

PREDISPOSING CAUSES.

Among predisposing causes may be mentioned:

Age.—The disease occurs at all ages, and has been seen in the infant at the breast as well as in the octogenarian. It is probably most usual between 20 and about 40 years. It is, however, by no means infrequent in children.

Sex.—It is frequently said by foreign authors that sex exerts no influence. In the United States, however, it can hardly be doubted that the disease is more frequent in the female, and, in the Southern States, the negro female.

Race.—This does not seem a factor of great importance. Reference has just been made, however, to the incidence of the disease in the negro.

Occupation.—In Italy undoubtedly the field laborer is the greatest sufferer from the disease; and it is the rural population among whom the disease is largely found in other countries of Europe. There are reasons, however, for thinking that such is not the case in America, the disease being frequent among well-to-do town and city dwellers.

In the pellagrous sections of Europe the field laborer subsists largely on corn in some form; in Italy it is polenta.

Alcoholism, previous illness, depression, hygienic conditions, etc.—It is a fact which has been noted by all observers that pellagra is often a secondary disease, engrafted upon some previous illness or depressing condition. It not infrequently follows pregnancy or lactation.

A history of alcoholism is often obtained from the sufferer. In the foreign literature of pellagra much is said of an "ethylic pellagra," which is by some regarded as a pseudo-pellagra. It is a zeist idea that alcohol distilled from spoiled corn may contain pellagrogenous toxins.

The disease in Europe is usually found in association with wretched poverty and poor hygienic conditions, but this does not seem so in America.

Climate and seasons.—Pellagra is not confined to the tropical zone, but it has been found only in the comparatively warmer parts of the earth. Apparently it does not occur in cold latitudes. The disease has the remarkable characteristic of showing definite seasonal exacerbations, and the actinic rays of the sun undoubtedly act as an exciting cause in the production of the erythema. The relation of the disease to the seasons and the sun's rays is important, but not definitely understood.

Heredity.—The disease is believed to be hereditary by many writers, but this has been denied by others. This point needs further observation. It is difficult to determine satisfactorily.

Contagion.—The contagiousness of pellagra may best be mentioned at this point. This has very naturally been a matter of much concern. So long as the etiology of the disease is unknown, it is of course impossible to make positive statements, but those who have had longest experience do not regard the disease as transmissible from one person to another. In Italy no precautions of quarantine or isolation are practiced, and the sick associate intimately with the well. Doctors, nurses, and others in attendance on the sick do not contract the disease. In the present state of our knowledge, measures of quarantine or isolation do not seem to the writer wise or necessary. They serve only to increase an already widespread pellagraphobia.

If communicable at all pellagra certainly does not seem to be so in any very direct way from one individual to another. Evidence is not lacking that pellagra is possibly a disease of place or locality, somewhat after the apparent nature of beriberi. This, however, does not necessarily imply anything as to its transmissibility.

PATHOLOGIC ANATOMY.

The morbid anatomy is neither constant nor characteristic. In a disease presenting such a variety of symptoms and characterized by such great chronicity, with the frequent presence of intercurrent affections and senile evolutionary changes, one could hardly expect to find a definite, single, morbid condition, and must learn to discriminate the manifold, accidental changes so frequently found.

Tuczek¹ describes as part appearances of cachexia the following: Wasting of adipose and muscular tissues, brittleness of the bones (fragilitas ossium), atrophy and fatty degenerations of the internal organs (chiefly those innervated by the vagus), heart, kidneys, spleen, intestines, liver, and lungs.

He also describes three further groups of morbid changes: (1) Intestinal: Atrophy of muscular coat, with occasional hyperemia and

¹ Klinische und anatomische Studien über die Pellagra, Berlin, 1893; and Tuke's Dictionary of Psychological Medicine, Philadelphia, 1892.

ulceration of the lower part of the tract; (2) abnormal pigmentation (similar to senile change), especially of ganglionic cells, heart musculature (brown atrophy), hepatic cells, and spleen; (3) alterations in the nervous system. The variously described conditions of hyperemia, anemia, edema, and at times inflammatory affections of the central nervous system and its coverings, together with the obliteration of the central canal of the cord, he regards as not peculiar to pellagra, but as accompanying conditions present in many chronic affections of the central nervous system and in senility.

The findings in the brain are in most cases negative except for occasional fatty degeneration or calcification of the intima of small blood vessels and pigmentation in the adventitial coats. In cases where a long-continued psychosis has led to a high degree of imbecility atrophy of the cerebrum may be found. In the cord the changes are fairly constant and important; degenerations in the lateral columns in the dorsal region and in the posterior columns in the cervical and dorsal regions. Very few changes are found in the lumbar cord.

With regard to degenerative changes in the peripheral nerves, he thinks such changes should be viewed with caution, when one considers their great frequency in chronic illness of many kinds.

He says further:

Microscopically, the affection seems to be a primary degeneration of the nerve fibers, with secondary proliferation of the neuroglia, the walls of the vessels not being necessarily implicated. Sometimes granular cells, and more frequently amylaceous corpuscles, are met with in the degenerated areas. Degeneration of the anterior root fibers along the anterior cornua has also been demonstrated, while there is to be found in addition a more or less considerable degree of pigment atrophy of the ganglion cells in the anterior cornua, with sclerosis of the matrix and atrophy of the nerve roots. Besides the excessive pigmentary deposit found in the peripheral ganglia, both spinal and sympathetic, there are no characteristic microscopical evidences in other parts of the nervous system.

Typhus pellagrosus furnishes us with definite post mortem results, chronic gastro-enteritis with formation of ulcers and swelling of the mesenteric glands and well marked changes in the central nervous system, associated with secondary affections of the kidneys, lungs, pleuræ, etc., being the main features on examination. It is to be noted that the spleen is usually involved in the general visceral atrophy and is never enlarged.

He draws a strong analogy between pellagra and ergotism both etiologically and pathologically.

Lombroso,¹ from observations on 113 necropsies, thus sums up the pathology of pellagra:

There are found irritations, exudations, and hyperemias localized more commonly in the membranes of the brain, spleen, liver, kidneys, inferior portions of the intestines, and above all in the spinal cord and its coverings.

¹ Trattato profilattico e clinico dela pellagra, Turin, 1892.

Atrophy of many organs occurs, especially those innervated by the pneumogastric—heart, kidneys, spleen, liver, intestines, and lungs. Besides these, the ribs and the muscles. Brown atrophy of the heart with cellular infiltration and diminution of weight was found frequently in the absence of general marasmus, and this, with other visceral atrophies, is common even in well nourished individuals. Fragility of the bones is ordinarily confined to the ribs. Fatty degeneration of the muscles is infrequent, and then usually confined to certain muscle groups.

Fatty degenerations are common, and such changes are observed in the kidneys, liver, and at times in the heart, and, what is of more import, in the spinal and cerebral vessels.

Very characteristic of pellagra is the great frequency of pigmentary degenerations. Thus, as noted, one finds brown atrophy of the heart, which is an atrophy with pigmentation, pigmentation of the liver cells, and sometimes pigmentation of the cerebral vessels and of the spinal and ganglionic cells, with or without fatty degeneration. In one case was seen a general pigmentation of the kidneys, the heart, the liver, and the vessels of the brain (hemolytic cellular disintegration).

There are rarely also other forms of anatomic degeneration, such as calcereous degeneration of the cerebral vessels and at times aneurysmal dilatations. These alterations, together with the thickening of the membranes of the brain and of its vessels, suffice to explain the psychic troubles so frequently met with.

To be noted finally is the tendency to precocious senility, with atheroma, a great number of amylaceous bodies in the spinal cord and in the sympathetic ganglia, precocious baldness and scleroses and pigmentation of the ectodermic structures.

Much importance is attributed by Lombroso and some other writers to changes formed in the sympathetic system.

Extensive and detailed reports on the pathologic anatomy of pellagra from American observers are as yet wanting. It has, however, been shown by several workers that the American disease pathologically shows no essential deviation from Italian pellagra. The morbid anatomy of the disease is nevertheless important, and the work needs a careful revision with modern methods.

EPIDEMIOLOGY.

The epidemiology of pellagra, like so many other features of the disease, is not well known. This phase of the subject has of late attracted much attention, and observations of this character are now of great importance.

The epidemiological data at present recorded for the malady rest largely on studies made in Italy. There is reason to think that perhaps some of these observations may not be in accord with what occurs in the United States. Time and work alone can determine

this. In addition to the many epidemiological facts and observations mentioned elsewhere in this bulletin, it is desired briefly to notice here one or two others. Space does not permit any general discussion of epidemiology.

In the first place, pellagra is essentially an endemic disease, but also shows the characteristics of affecting at times large numbers of persons, of extending its area to some extent, and of appearing in new places remote from its known endemic centers, so that it may with justice probably also be called epidemic. It has never shown, however, any of the characteristics of the great epidemic diseases, and is never pandemic.

Disregarding, for the present, any hypothesis as to the cause of the disease, the work of Sambon and of Alessandrini has brought out sharply the probability that the disease is one of place or locality. Investigating pellagra in Italy, the writer has repeatedly been impressed with the fact that so many physicians, in pellagra districts, assert that all of their cases of the disease come from this or that restricted locality. This observation has to some extent been confirmed in the United States, but as yet the number of such observations is too few for a final conclusion. Should further work confirm this observation, and show it to be a general characteristic of the disease, it would certainly be a decided step in advance.

It may be noted also that both Sambon and Alessandrini connect the disease with water. Terni and Fiorani¹ have recently made a similar observation. Such an idea may also be found among some of the older writers, and in the United States also some such idea prevails to a slight extent. There are wide differences of opinion, however, as to the nature of the relation.

Finally, there is the old question: Is there a pellagra without maize? Certainly the most pronounced zeist can not deny that numerous cases of pellagra have been reported by credible observers in whom there is no history or evidence of the consumption of this cereal. The real question, however, is whether there exists an endemic pellagra unassociated with maize. Reports of such from Spain are not credited by the Italian zeists, who still claim that endemic pellagra unassociated with a maize diet does not exist. It may be pointed out that maize is very extensively cultivated over the earth's surface, and to say that a disease does not occur except where this cereal is used as food is to make a very broad statement. A premise which includes too much weakens the conclusion.²

SYMPTOMATOLOGY.

Pellagra is an endemic disease characterized pathologically by serious organic changes in the central nervous system, and clinically

¹ Rivista Pellagologica Italiana, March, 1910.

² See Public Health Reports, P. H. and M. H. Service, XXVI, 39, Sept. 29, 1911.

by a chronic course with the periodic manifestations of acute phenomena referable to the gastrointestinal tract and the nervous system as well as by the appearance of an erythematous exanthem on certain exposed body surfaces. It not infrequently leads to insanity or to a fatal cachexia.

To give any clear and succinct description of a disease so protean in its manifestations is by no means easy. Almost all writers seem to have been impressed with this fact, and hence Lombroso's epigram, "There is no disease; only the diseased." Pellagra is, however, a definite, morbid entity, and many consistent descriptions have been given of the disease.

Largely for purposes of description, writers for a long time have divided its symptoms into stages or periods, much as we do with syphilis. Many different divisions have been suggested, but since all of them are largely artificial, none seems entirely satisfactory. Perhaps, therefore, it is just as well to make use of the simplest—prodromal, first, second, and third stages. It should not be forgotten, however, that such a division is, to a large extent, arbitrary; that there is no sharp line of demarcation between the various stages; that nothing is implied as to the length of time the disease may have existed; and that the various stages represent rather differences in degree than in kind. The disease is essentially chronic, but is not, of course, always uniform in the rapidity of its development and evolution. Reference is often made to acute or florid types of pellagra, but such references apply to certain acute incidents which may occur in its chronic course. These will be described later. An acute pellagra, *ab initio*, probably does not exist.

Remembering, then, that the disease is chronic and that there is no definite length of time or regular succession about the various stages, the following general statements may be made:

The prodromal stage often consists of little more than vague symptoms and a feeling of general malaise. The first stage has reference to the gastrointestinal and skin symptoms. The second stage includes the cerebrospinal and psychic phenomena. The third stage is the terminal one, characterized by cachexia. It may be noted here that pellagra is often spoken of as wet or dry. These terms are more convenient than scientific and have reference to the differences in the erythema. One form remains dry and scaly; the other develops bullæ and is associated frequently with grave constitutional disturbances.

Pellagra runs its course in a series of periodic attacks—alternating ameliorations and exacerbations. The exacerbations occur as a rule in the spring, sometimes in the fall, and subside after a time, only to recur again the next year. Following the somewhat indefinite prodromal period, there arise next gastrointestinal and nervous dis-

orders, usually accompanied in a short while by the striking erythema. The brunt of the successive attacks is borne by the nervous system, and each annual recurrence leaves a deeper and more ineradicable impression upon the nervous and mental condition of the sufferer. At the outset it is to be emphasized that while the erythema is the striking symptom of the disease, the essential morbid process involves the central nervous system. This conception of the malady is fundamental.

PRODROMAL STAGE.

The prodromal stage is indefinite both in length of time and symptomatology. Patients may complain of fleeting pains and various paresthesias. Neurasthenic symptoms may be present, and it is important to remember that such symptoms may represent a prodrome of pellagra.

There may be complaint of burning in the mouth and stomach with occasional stomatitis or ptyalism.

Progressive weakness, especially of the lower extremities, may appear weeks or months before the erythema. There may be loss of appetite and a feeling of general malaise. Sometimes there is vertigo. The prodromal stage is not so often seen. As a rule the patient presents himself with the developed disease. Pronounced symptoms usually appear in early spring, sometimes fall, the time incidence varying in accordance with the weather—April to June and September to October.

FIRST STAGE.

The first stage usually begins with gastrointestinal disturbances. There is a sensation of heat in the mouth and stomach, taste is altered, appetite usually lost, but there may be bulimia, and ptyalism is often present. The tongue is coated centrally and red and smooth at the tip and edges. The papillæ are frequently prominent and injected, and in the negro occasionally blackish, giving the organ a stippled appearance. Sometimes the tongue is smooth and red, denuded of its superficial epithelial coat—the “bald” tongue, or, if very red, the “cardinal” tongue. At other times the papillæ over the upper surface are very long, giving a heavy coating, which splits in places to form fissures, and then we have the “checkerboard” tongue. Appearances thus vary, but the tongue in pellagra is to some extent characteristic. An examination of the mouth will often show general redness of the mucous membrane, with vesiculation or even superficial ulceration. Dyspeptic symptoms, with flatulency and abdominal distention, are noted, and sometimes abdominal pain. Occasional vomiting may occur, especially in alcoholics. Diarrhea is frequent, at

times constipation, and the diarrhea, as well as the vomiting, may in some cases be of a spasmodic type. Sometimes it is dysenteric in character, muco-sanguinolent, with colic and tenesmus.

Muscular weakness, especially of the lower extremities, is usually evident early, and patients tire very easily.

The temperature is normal, though there may be a slight evening rise. If there is much fever complications should be sought for. Ordinarily in pellagra there is little fever. The pulse may be accelerated, though at times slow. Functional heart murmurs may occur, but should be sought later.

Vertigo is often present and very annoying; headache, usually occipital, is frequent, and often severe; rebellious insomnia occurs; various neuralgias are not seldom in evidence, and especial stress is laid by some on spinal neuralgias, with cramplike pains extending to the extremities. The knee jerks at this stage are usually exaggerated.

Intelligence, even at this early period, is often affected, and there is mild mental weakness with depression of spirits. Neurasthenic manifestations are frequent and important.

The blood and urine show the changes described later.

Along with these symptoms the characteristic erythema appears, selecting nearly always the uncovered parts of the body, and being symmetrical in its distribution. Its appearance is usually accompanied by a sensation of heat and swelling, with slight itching, in the affected parts. The itching of the erythema is never marked.

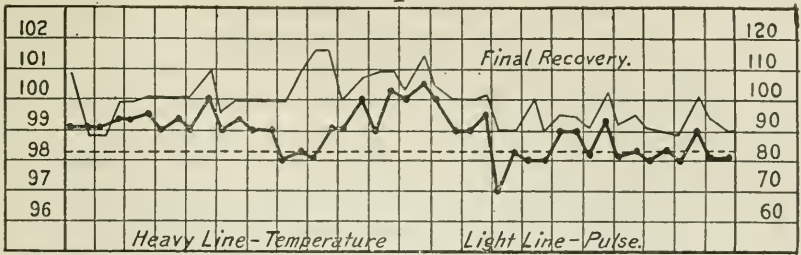
SECOND STAGE.

While erythema, digestive, and some nervous disturbances characterize the first stage, the second is marked by an aggravation of all of these symptoms and the appearance of new and marked evidences of involvement of the nervous system which now dominate the scene. The characteristics of this stage are serious cerebrospinal disturbances which, following largely Scheube's¹ description, may be thus enumerated:

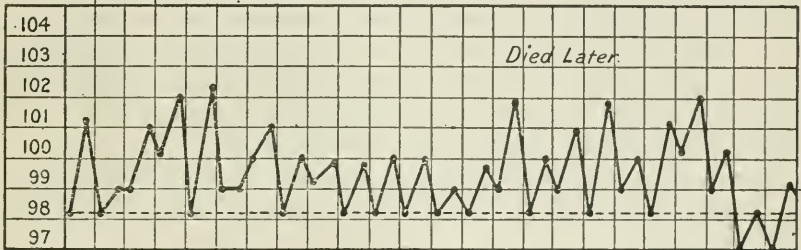
Motor disturbances.—There is usually considerable muscular weakness, especially of the lower extremities, and not infrequently partial paralyses are observed. Among motor symptoms of irritation may be seen muscular tension and tonic contractions in the extremities, which sometimes increase to tetanic rigidity. There may also occur tremor of the arms, head, and tongue, as well as cramplike seizures and convulsive movements. Exceptionally have been noted epileptiform convulsions with loss of consciousness.

¹ Diseases of Warm Countries. Philadelphia, 1902.

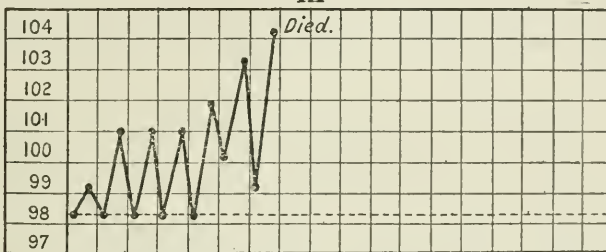
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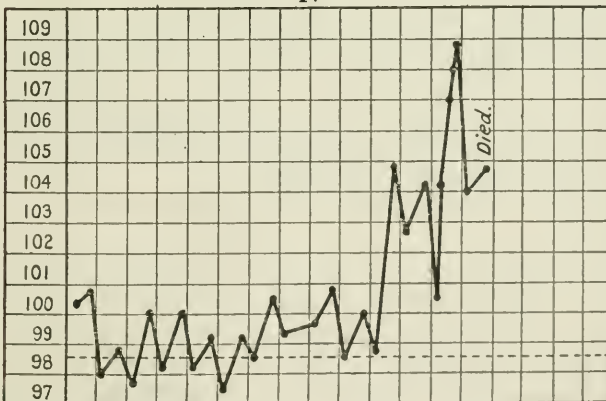
II



III



IV



I. Ordinary temperature curve. II. Erythema of the wet type. III. Typhoid pellagra; tetanoid state; early death. IV. Terminal acute delirium with hyperpyrexia. All temperatures Fahrenheit, and recorded twice daily.

(From Pellagra, by A. Marie, trans. by Lavinder and Babcock, slightly modified.)

(Courtesy of the publishers, The State Company, Columbia, S. C.)

The gait is paralytic or paralytic-spastic. Ataxia is said not to be observed. Partial muscular atrophy may appear, and the disease may simulate amyotrophic lateral sclerosis. The muscles show no important or constant reactions to electric stimulation, but their mechanical excitability is increased.

Sensory disturbances.—The sensibility of the skin varies. The sense of touch and temperature remains intact, the sense of pain is sometimes diminished. The muscular sense is normal.

Paresthesias are frequent and of great diversity. Sensations of burning, especially on the extremities, are most often complained of, and are described as so intolerable in some cases as to result in suicide. There are also sensations of formication, hot and cold flushes, numbness, burning of the eyes, dragging in the neck, suffocation, a girdle around the body, heaviness in the groins and uterus, peculiar feelings in the penis, and heaviness of the testicles.

There may occur neuralgic pains in the head, neck, and back, and sensitiveness to pressure is described over the spine, especially in the dorsal region.

With regard to reflex activity, the skin reflexes are usually normal. The tendon reflexes, especially the knee jerks, are ordinarily much increased, but may be weak or absent. They are often unequal on the two sides.

Organs of special sense.—Occasionally are seen weakness of vision, diplopia, photophobia, and other ocular disturbances. Pupillary reactions are often indolent, dilatation, more rarely contraction, is observed, and such disorders may be unilateral. Organic changes may occur and conjunctivitis is seen at times. The sense of taste is sometimes perverted. A salty taste has been so frequent in parts of Italy as to give the popular name *salso* to the disease.

Vasomotor and trophic changes.—General contraction of the cutaneous vessels with sensations of cold are encountered, and sometimes goose skin may be found. During the later stages a neuro-paralytic dilatation of the cutaneous vessels may arise, with possible edema. The face at times assumes the alcoholic appearance. The nails may show disorders of nutrition.

The changes associated with the erythema have been described elsewhere.

Psychic disorders.—It has long been recognized that the mental condition of sufferers from pellagra frequently undergoes an early modification. This condition may be ill defined or show itself by a greater psychic excitability, indicating a lowered inhibitory power. Again the patient may be depressed or neurasthenic. Later distinct psychoses may develop. These manifestations are probably toxic in their nature. This is an important phase of the disease and will be

found mentioned under pellagrous insanity. For fuller information the reader must consult more extensive works.¹

General symptoms.—Fever in uncomplicated cases is slight. Cases with the wet erythemas, however, usually have temperature. The pulse shows nothing characteristic. The gums sometimes display the scorbutic condition. The acidity of the gastric juice is diminished. There is usually decided loss of weight. Signs of premature senility—baldness, gray hair, arteriosclerotic changes, etc.—are frequently observed. Disturbances of the menstrual function and other disorders of the reproductive system are not infrequent. If their true significance is overlooked they may lead to useless, if not harmful, surgical procedures.²

The blood shows the changes common to a secondary anemia, but very marked anemias are not frequently seen. In addition to this there is seldom any leucocytosis; on the contrary, leucopenia is not infrequent. The leucocyte formula is somewhat disturbed, and there is described a relative large mononuclear increase. This, however, is denied by some writers. The urine is seldom much diminished in quantity. It is often of low specific gravity. Its acidity is frequently diminished and it may be alkaline in reaction. Indican is excessive in a great many cases. The diazo reaction occasionally appears. An albuminuria, with an associated nephritis, is not seldom met with.

Lombroso and Roncorini found the urea, chlorides, and phosphates diminished.

THIRD STAGE.

This is really the terminal stage and is chiefly characterized by cachexia. The symptoms already described do not give place to new ones, but, on the contrary, they are present and aggravated. The cachexia now, however, stands boldly in the foreground, with dementia, paralyses, and other cerebrospinal phenomena still prominent in the picture.

There is an increasing marasmus, with marked anemia, atrophy of subcutaneous fat and musculature, and a lack of resistance against intercurrent diseases. In addition there are great muscular feebleness, perhaps paralyses, including the bladder, and an uncontrollable, painless, serous diarrhoea. Death follows, with the signs of heart weakness and its consequences, edema, and effusions; or some intercurrent disease, such as acute tuberculosis of lungs, which is common at this period, or septicemia following decubitus, may close the scene.

¹ See J. W. Babcock's *Psychology of Pellagra*, Journ. S. C. Med. Association, November, 1910; and Proceedings American Medico-Psychological Association, 1910. An excellent brief article with bibliography.

² See Saunders, E. B. The gynaecological, obstetrical and surgical aspects of pellagra. Transactions National Conference on Pellagra, Columbia, S. C., 1909, and American Journal Insanity, LXVII, 3, 1911.

THE PELLAGROUS ERYTHEMA.

The erythema¹ is the characteristic symptom of the disease. It makes its appearance usually in the springtime, sometimes in the fall. It appears symmetrically and on the uncovered parts, selecting at first especially the extensor surfaces, backs of hands and forearms, face, back of neck, upper chest, and dorsal surfaces of feet. Later the flexor surfaces may become involved, but the palmar and plantar surfaces frequently escape. Cases are, however, seen with the erythema on the covered parts of the body, and rarely it may be generalized.

Its relation to the sun's rays has been a subject of much discussion, but the most generally accepted idea is that the actinic rays of the sun simply act as an exciting cause in persons already victims of the disease.

It usually makes its first appearance on the backs of the hands, developing later in other places. The skin in the beginning becomes red with sensations of burning and perhaps slight itching, and usually some puffiness is observed—all very similar in appearance to a marked sunburn. This red color disappears on pressure, but promptly returns when pressure is released. After some days bullæ may appear, and these may fuse into large plaques filled with serum, or even seropurulent or sanguinolent fluid. The edema may then disappear, the epidermis dries and falls in small, grayish scales. This bullous, or wet erythema, is not infrequent in the United States, and is ordinarily accompanied by serious constitutional symptoms. Locally it sometimes results in extensive loss of the epithelial layer of the skin, with almost necessarily secondary infections and a distressing condition, which requires much attention. At other times the epidermis, after the initial redness described, may take on a dark color, described as brownish or blackish, chocolate colored, or plum colored, after which it dries and scales, with no bullous formation. Desquamation without erythema has been reported; also pustular erythema, especially on the face. Among some exfoliation may occur in large flakes. After the first attack the skin remains pigmented for some time, and as repeated attacks occur it gradually undergoes chronic thickening with pigmentation, often of a dirty yellow, yellowish green, or bronzed color. The skin is then indurated, thickened, hard, and rough. Later its elasticity partially disappears, the articular folds grow deeper, painful fissures and thick crusts may develop, or even small ulcerations after exfoliation. Ecchymotic spots may sometimes be seen. After repeated attacks the skin, especially of the hands, may become atrophic, thin, and parchment-like.

¹ Howard Fox ("Personal observation on the skin symptoms of pellagra," *Medical Record*, Feb. 5, 1910) has questioned the accuracy of the term erythema for the pellagrous skin lesions and suggested its replacement by the term dermatitis.



ILLINOIS CASE.—ERYTHEMA ON HANDS, FOREARMS, AND NECK. NOTE THE MARKED SYMMETRY.
Courtesy of Dr. George A. Zeller, Superintendent Peoria State Hospital, Peoria, Ill.

with almost entire loss of elasticity, and show whitish spots like the *striae gravidarum*. When compared with the skin of the rest of the body the difference is then striking.

Merk¹ has summed up the distinctive characteristics of the erythema briefly thus:

(1) An eruption which is an erythema in the dermatologic sense of that word, comparable to the *erythema exsudativum multiforme* of Hebra, and also to certain toxic, endemic, erythemas like lupine disease in animals, the so-called clover disease, and buckwheat erythema (*fagopyrismus*); also lathyrism and ergotism.

(2) The eruption appears suddenly, and its genesis is not necessarily connected with atmospheric or solar influences.

(3) Its limitations are peculiarly typical—sharp with red border—and as it develops it shows a more or less broad zone of scaling with a peculiar color.

(4) The eruption does not reach its height for many days or weeks, and requires a still longer time for its retrogression (several weeks). First there occurs loss of the rosy border, then the center gradually fades, while the scaly, crusty zone remains for a long while the seat of the receding process. The changes in the central zone vary with location, but are always characteristic of an erythema.

(5) By its external characteristics the erythema is strongly allied to the so-called hyperkeratosis. Still, especially on the dorsal surfaces of the hands, the erythema may show enormous exudations.

(6) The erythema is nearly always remarkably symmetrical, and shows certain places of predilection—first, backs of hands ("glove"), more rarely backs of feet ("boot"), still more rarely the face ("mask"), and finally the neck (Casal's "neckband" and "cravat"); in the second place, the female genitalia and perineal region. It is also seen in asymmetrical, isolated situations, as elbows, knees, axillary folds.

(7) Some time after its appearance the erythema shows the typical, dirty gray-brown color of changes peculiar to hyperkeratosis. At the same time the bright red of the erythema may be seen through this, and gives to the whole a kind of bronze coloring which is especially sharp during the retrogression of the process.

(8) In an individual it appears as a rule only once annually, generally, but not necessarily, in springtime. The following year it recurs, and finally leads to atrophic changes, especially on the backs of the hands.

DURATION.

As stated, the disease is essentially chronic in its nature, but shows acute phenomena in the spring and less often in the fall. Its duration is indeterminate, and there is no regularity about the succession

¹ Verhandl. der Gesellsch. deut. Naturf. u. Aerzte. Versamml. 77, 1905.

of the various stages. A pellagrin may be very ill one year and suffer lightly the next. The disease in some may remain almost stationary in the first stage for many years, while in others it may reach the second, or even the third, in the course of a few months.

A great many cases in the United States have been characterized by rather rapid development with the early appearance of grave conditions. This intensity of the American disease has been noted by nearly all observers, and is in marked contrast with the disease as now observed in Italy. Even in the United States, however, cases are not infrequently seen which have existed some years.

FORMS OF PELLAGRA.

In a disease so varied in its manifestations as pellagra one or more symptoms may dominate the clinical picture, and so permit artificial classifications. Many forms of the disease have been described and various divisions made. Most of these may be disregarded, but there are two conditions which deserve some consideration.

Typhoid pellagra (*typhus pellagrosus*).—This condition is one of the important and striking manifestations of pellagra. The name is somewhat unfortunate, as it is not a typhoidal condition, nor is it related to the specific disease, typhoid fever, which is sometimes seen, however, as a complication of pellagra. It is an acute explosion which is peculiar to pellagra, and occurs as an incident in the chronic course of this disease. It is thus described in the graphic language of Belmondo,¹ who has made especial studies of this condition:

It is rare that typhoid pellagra develops suddenly, for, as a rule, the ordinary symptoms of pellagra show a characteristic intensity; the enteritis and the nervous phenomena (neurasthenia and paresis), as well as the general weakness, assume an unwonted importance, and even on the psychic side there are a clouding of consciousness, depressed tone, and a tendency to suicide.

Most of the cases are poorly nourished and at times much emaciated; however, there are others in which the panniculus adiposus is abundant and the general development of the muscles remains almost normal. There is often almost absolute unconsciousness, at times verbigitation or visual hallucinations of a terrifying nature.

The entire musculature is in a very pronounced state of tonic contraction, and there is marked rigidity evident on making passive movements of the extremities. In these manifestations the reflex rigidity increases and generally the passive movements ultimately become impossible. Often the patient makes spontaneous, inco-ordinate movements, especially with the hands and arms, from time to time. In these movements, apparently intentional, there is shown frequently a tremor of the upper extremities, with wide oscillations and a certain grade of ataxia. The speech is drawling, the voice trembling and often nasal.

¹ "Le alterazioni anat. del midollo spinale nella pellagra, etc." Riv. Sper. di Freniat., Reggio-Emilia, 1889 and 1890, XV and XVI.

The face has a rigid and contracted appearance; however, at intervals the mimic muscles, principally those of the mouth, are agitated by tremors which spread from one muscular fasciculus to another and reach even distant muscles.

The lower extremities are habitually in forced extension, the feet in plantar flexion. The exaggeration of the reflexes increases up to the last hour of life, the knee jerks being especially exaggerated. Even a definite ankle clonus is not rare. Under a light percussion on the tendon of the quadriceps there is often a spasmodic reaction of the leg, accompanied by convulsive movements of the whole body. At times, together with the plantar clonus, there is a paradoxical contraction of the extensors of the foot, and hyperesthesia to tactile stimuli so marked that a breath of air or a ray of light may provoke motor disorders or tonic convulsions.

To this it may be added that fever is the rule in this condition, the temperature being continuous, often with marked remissions, and usually high. Roscola is lacking. In most cases death occurs in one or two weeks, often in a terminal bronchitis.

Typhoid pellagra is not very frequent, but it is observed in America. There have been observed also certain allied acute states, usually fatal, which do not display all of the above-described symptomatology.

Pellagra sine pellagra.—Strambio recognized a pellagra without skin manifestations, and the Italians do not hesitate to make such diagnoses. Roussel doubted whether there ever occurred a pellagra without skin lesions at some time in the course of the disease.

Certainly cases of the disease may be under observation for a long while without the appearance of an erythema. Diagnosis must, however, often be difficult and uncertain, and should be made with caution. A tentative diagnosis, with the institution of treatment, would be safer.

Harris¹ has recently discussed this condition as seen in the United States.

PELLAGROUS INSANITY.

The association of mental phenomena with pellagra is a matter of much importance. In Italy it has been variously estimated that from 4 to 10 per cent of pellagrins become insane. It is now well established that this relationship is that of direct cause and effect and not an accident or coincidence.

In the United States up to the present time there are no data in existence which will give us a definite idea of the ratio between sane and insane pellagrins, but the number of cases with mental disturbance is undoubtedly large. This highly important phase of the subject, which can only be touched upon in a paper of this character, has been briefly summarized as follows:²

From observation and study of the subject in America it would appear that while depression (melancholia), stupor, and mutism are the ordinary psychic

¹ The diagnosis of pellagra. American Journal of the Medical Sciences, May, 1911.

² Pellagra: Marie, translated by Lavinder and Babcock, Columbia, S. C., 1910.

expressions of the pellagrous intoxication, yet excitement (mania, exaltation) occurs under different conditions. First, we may have temporary episodes of excitement lasting only a few hours or a few days. Second, an acute, collapse delirium may occur at any stage of the malady and usually terminates in death in from one to two weeks. It may even be an initial delirium (this is not uncommon in the United States, and it is sometimes called acute pellagra). Third, typhoid pellagra which occurs as a terminal phase of chronic pellagra. It is rare in Italy and far from frequent in the United States.

Strictly there appears to be no mental symptom-complex characteristic of pellagra, but pellagra may act as the exciting cause of several different nervous and mental states. These are: Neurasthenia, hysteria, polyneuritis, meningitis, epilepsy, acute confusional insanity (including stupor, hallucinosis, collapse delirium, and katatonia), anxiety psychoses, and the manic-depressive group, pellagrous pseudo-general paralysis, and several other forms of dementia.

It is not unlikely that the mental symptoms of pellagra may differ by seasons, or in different countries and in different parts of the same country, just as, broadly speaking, do the physical signs and symptoms of the disease.

The tendency of pellagrins to suicide has been dwelt upon from the time of Strambio by many writers and observers. Our experience in America is beginning to teach us how painfully true this observation is.

The protean and often paradoxical expressions of this strange malady deserve emphasis and the clinician is warned to be on the alert for many unexpected nervous and mental phenomena when dealing with pellagra.

PSEUDO-PELLAGRA.

In the foreign literature of pellagra one is constantly reminded that there are false or pseudo-pellagras which must be carefully distinguished from the true disease. References to such conditions in American literature are rather conspicuous by their absence.

Roussel, in a controversy with some of his confrères, first made use of this word to describe certain states which resembled pellagara, but which on careful analysis, in his opinion, showed essential differences from that disease. In some respects the introduction of the word has been unfortunate, and it has proven a cause of confusion to many and an object of ridicule to others. The antizeists assert that pseudo-pellagra is the kind of pellagra which the zeists can not make conform to their maize theory; while, on the other hand, the zeists seem convinced that there are certain morbid conditions, closely simulating pellagra, which yet do not permit that diagnosis.

The diagnosis of pellagra is not always easy. Indeed it is not infrequently difficult, and in the absence of any laboratory or other procedure by which it may be definitely determined, there are frequent occasions for confusion. It is possible, of course, but rather unlikely, that more than one morbid entity may at present be included under pellagra. The determination of such a question must await more definite etiologic knowledge.

DIAGNOSIS.

The diagnosis of pellagra in well-marked cases with both the skin manifestations and the constitutional phenomena in evidence—the

so-called pellagrous triad of erythema, nervous and digestive disturbances—should offer no difficulty. Yet, in spite of its striking characteristics, instances are not infrequent in parts of the United States to-day where competent diagnosticians fail to recognize the disease, even in pronounced cases. Such errors can be attributed only to ignorance of its symptomatology and inattention to the literature of the current journals.

The diagnosis in many cases, and especially the early diagnosis, is frequently difficult, and in cases which do not present skin manifestations—pellagra sine pellagra—it must very often be tentative. Careful inquiry into the history of the case and a search for pigmentation or other evidence of a previous skin lesion will often be of aid. The erythema is of first importance in the diagnosis and, according to Merk, possesses the same value as does the exanthem of scarlatina, measles, varicella, and variola in the respective diagnoses of these diseases. There is no laboratory or other definite method of making the diagnosis and dependence must be placed on the general symptomatology.

In the differential diagnosis ergotism, lathyrism, and acrodynia are often spoken of, but are not likely to cause confusion in this country. Scurvy, leprosy, and beriberi are also mentioned, but in most cases should be easily discriminated. Occasional cases of sprue may be met with in the United States and should be kept in mind.

Various skin lesions, such as solar erythema, lichen, eczemas, and erythema multiforme are important. The differentiation must be made on local appearances and general symptomatology.

Dementia paralytica and certain functional neuroses may cause confusion. Neurasthenia is especially to be kept in mind.

Typhoid pellagra and allied acute conditions may be mistaken for an acute infectious disease, uremia, or diabetic coma. The history of the case is of importance; and the temperature curve, condition of internal organs, and development of the process will be of service in arriving at a conclusion.

PROGNOSIS.

The prognosis of pellagra in America is undoubtedly serious. The disease here has been marked by an intensity not seen in the Italian pellagra of to-day, and foreign statistics furnish us with no reliable guide. The case mortality in the United States is probably diminishing. It still remains high, however, and doubtless exceeds 25 per cent.

Certain considerations are of importance. The opinion is almost unanimous that early cases offer the most hopeful results from treatment; and early diagnosis has therefore a definite bearing on prognosis. The disease is essentially chronic and, untreated, advances in-

exorably. With ultimate serious involvement of the central nervous system the outlook is not promising. Mental involvement also adds to the gravity of the case.

Pellagra is not a febrile disease, and the occurrence of fever, especially if high or constant, must be regarded as a danger signal. The character and extent of the skin manifestations have long been thought to bear no relation to the constitutional disturbance, but cases with a bullous or wet type of erythema usually show grave general symptoms. Steadily progressing emaciation, especially if accompanied by an inveterate diarrhea, often ends fatally.

Complications are of importance and their presence should not be overlooked in prognosis. Intestinal parasites, nephritis, bronchitis, pneumonia, decubitus gangrene, and tubercle should be borne in mind. The occurrence of such complications of course adds to the seriousness of the situation.

It is to be especially noted that pellagra is characterized not infrequently by the rather sudden appearance of grave acute phenomena, such as typhoid pellagra and allied conditions. These states are of the utmost gravity, and usually lead to a fatal result. The possibility of their occurrence should not be forgotten. Occasionally very sudden death may occur in cases unassociated with these conditions.

Apparent recovery from the disease is likely to be followed by a recrudescence, sooner or later, and all patients should remain under medical supervision for a long period of time.

TREATMENT.

The treatment includes prophylaxis and the management of the developed disease.

Prophylaxis.—The lack of definite knowledge regarding the etiology of the malady renders all prophylactic measures of doubtful value. Damaged corn, however, can certainly not be considered a suitable article of diet, and such corn should not under any circumstances be used as food for human beings. There is undoubtedly no little corn of this kind on the market, and its elimination as an article of food can be advised on general principles alone. Further than this, in the present state of our knowledge, the writer feels inclined to give the patient the benefit of the doubt and advise those who suffer from the disease to avoid the use of all corn products, good or bad.

It may be stated here that under the national law of 1902 the Italian Government has instituted a number of prophylactic measures against pellagra, all based on the assumption that the disease is due to spoiled corn. These measures include inspections of corn, reports of the disease, special hospitals, sanitary stations, special bakeries, educational propaganda, and many other things. As a



EGYPTIAN PELLAGRA.



ITALIAN PELLAGRA.

From Pellagra, by A. Marie (translated by Lavender and Babcock), slightly modified. Courtesy of the Publishers, The State Company, Columbia S. C.

result of this work it is claimed that the disease has been much reduced both in numbers and intensity.

Management of the disease.—There is no specific for pellagra, and the treatment is to a great extent symptomatic. Experience is teaching us, however, that careful attention to details will often produce surprisingly good results. Space permits only a brief outline of the essential points in the treatment.

General measures.—Rest is a matter of prime importance. Severe cases, and all cases with acute symptoms, should be in bed; and even in mild cases careful attention should be given to this point. It can not be too much emphasized, and should be continued through convalescence for at least part of the day.

Diet is a matter of almost equal importance. It should be abundant, carefully selected, easily assimilable, and, whenever possible, should include meats. It must, of course, be regulated to meet the needs of the individual case, but abundance of food must be insisted upon. Eggs and milk can, of course, be made use of, and sugar can often be added with benefit. Care should be taken to include a liberal supply of salt. Sometimes an antiscorbutic diet seems of benefit. Corn and all corn products had best be prohibited. The patient should be weighed regularly. Increase in weight is of favorable significance.

Hydrotherapeutic measures may often be used with benefit. Cold and warm baths, simple or medicated, as well as douching may be employed. Such treatment must, of course, be used with discretion and consideration given to the state of the patient and the result to be obtained. Salt rubs are of benefit, and massage may often be employed as an adjuvant to the hydrotherapy. Enemata, simple or medicated, may be advantageously used for the diarrhea.

Change of climate, especially to colder latitudes, may at times be advised. Avoidance of strong direct sunlight will often prevent a bad erythema. Fresh air and cleanliness are of course to be enjoined.

Saline solution by the bowel may be of service, and such a solution intravenously may be of much service in severe cases like typhoid pellagra.

Medical.—Following Lombroso's teaching, arsenic has long enjoyed a reputation in the treatment of pellagra. It has not given the results in the United States that are claimed for it by the Italian and Roumanian observers. It is, however, of value, and deserves not to be neglected. Fowler's solution may be used in ascending and descending doses. The so-called arsenical preparations, like atoxyl, soamin, and arsacetin, may be used, and salvarsan certainly deserves a more extensive trial in carefully selected cases.

Hexamethylenamine and quinine have been recommended; also thyroid gland in some form has been used.

Symptomatic remedies must be used as needed. For insomnia, the bromides, chloral, paraldehyde, sulfonal, trional, and veronal; for the diarrhea, some of the bismuth preparations, atoxyl, guaiacol carbonate, ergot; for the anemia, some bland preparation of iron; for the erythema, a calamine lotion or a bland ointment, or, if necessary when there is exfoliation and infected raw surfaces, a moist antiseptic dressing. Strychnine is of value in convalescence. Symptoms must be met as they arise.

Complications, such as malaria, syphilis, and intestinal parasites, should be promptly treated with appropriate remedies. It is wise to examine the feces for the ova of parasites.

Surgical.—Cole¹ has directed attention to the value of the direct transfusion of blood in the treatment of pellagra. Under some circumstances it is doubtless a valuable surgical resource. The operation, however, requires surgical skill and experience.

In a few cases of pellagra in the United States appendicostomy, with subsequent flushing of the bowel, has been employed. Such treatment does not seem logical unless there be some complication such as amebiasis.

In conclusion, the mental depression so often associated with pellagra sometimes results in suicide, and this should always be kept in mind. It must also be remembered that pellagra is a disease which is very chronic in its nature, and patients even when apparently recovered should nevertheless be kept for a long while under medical supervision.

BIBLIOGRAPHY.

The literature of pellagra is extensive. Most of it is in Italian, French, German, and Spanish, but since the advent of the disease in the United States the English literature has rapidly accumulated. For those who desire to go thoroughly into the subject the Index-Catalogue of the Surgeon General's Library at Washington, and the volumes of the Index Medicus will be found indispensable.

Salveraglio (*Bibliografia della pellagra*, Gior. d. Soc. ital. d' Ig., Milano, 1887, IX, 1-156) has carefully compiled the literature up to 1887. In Marie's monograph on pellagra, as translated by Lavinder and Babcock, will be found an exhaustive compilation of the English literature up to 1910, as well as extensive references to foreign literature.

In the files of many American journals since 1907 will be found numerous articles on various phases of the disease. Brief articles may also be found in the recent editions of many medical works in English—works on tropical medicine, practice, diagnosis, skin diseases, mental and nervous diseases, as well as encyclopedias, reference handbooks, annual reviews, etc.

¹ Winthrop, G. J., and Cole, H. P. *New Orleans Medical and Surgical Journal*, LXIII, 90-97, 1910-11.

For the benefit of those who may desire to go a little more deeply into the subject, yet lack the time and opportunity for very extensive reading, there is given below, with critical comments, a brief list of literature. All of this may be found in the Surgeon General's Library, and some of it may be found in smaller collections.

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- CALMARZA, J. B. Estudios sobre la pelagra. Siglo Med., Madrid, 1869 and 1870, XVI and XVII.
- HUERTAS, F. La pelagra en España. Archivos Latinos de Medicina y de Biología, Madrid, año 1, núm. 1, October 20, 1903.

The Spanish literature of pellagra is not of great importance. Casal's paper is of much interest from an historical standpoint. The reference given above is to a very good Spanish translation of the original, which is in Latin. Calmarza's work is of interest. He has written a good deal on the subject. The reference given is to a prize essay, antizeist in tone. Huertas is one of the best modern writers, and appended to the reference given will be found a very good bibliography of the Spanish literature.

GERMAN.

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- . Das Krankheitsbild der Pellagra. Verhandl. der Gesellsch. deutsch. Naturforsch. und Aerzte. Versamml. 77, 1905.
- BABES, V. and SION V. Die Pellagra. In Nothnagel's Spec. Pathol. und Therapie, Wien., 1901, Bd. XXIV, Hft. II, Abt. II, III.
- GREGOR, A. Beiträge zur Kenntniss der pellagrösen Geistesstörungen. Jahrb. f. Psychiat. u. Neurol., Leipz. u. Wien, 1907, XXVIII, 215-309.
- MERK, L. Die Hauterscheinungen der Pellagra. Innsbruck, 1909.
- TUCZEK, F. Klinische und anatomische Studien über die Pellagra. Berlin, 1893.

The German literature is important. Neusser has had a rich opportunity for observation of the disease in Roumania, as well as in Italy. He is the creator of the autointoxication idea of the cause of the disease. His view is discussed in the first reference given. The second reference gives an excellent brief account of the clinical picture of the disease. The article by Babes and Sion is a very good one and contains a good bibliography. Gregor's work is among the best on the psychic side of the disease. Tuczek's studies on the pathology of the disease are well known. Merk's handsomely illustrated volume on the skin manifestations is a fine study.

FRENCH.

- ROUSSEL, TH. Traité de la pelagra et des pseudo-pellagres. Paris, 1866.
- BILLOD, E. Traité de la pelagrie. Paris, 1870.
- LANDOUZY, H. De la pelagrie sporadique. Paris, 1860.
- PROCOPIU, G. La pelagrie. Paris, 1903.
- TRILLER, B., La Pellagre, Paris, 1906.
- NICOLAS, J., and JAMBON, A. Contribution à l'étude de la pelagrie et du syndrome pelagrieux. Ann. de Dermat. et de Syph., Paris, 1908, 4. s., IX, 385-480.

The French literature is extensive. Roussel's work is a classic. It is perhaps the best single book in existence, but has a strong zeist bias. Billod and Lan-

douzy's work is important from the side of pseudo-pellagra. Procopiu's small monograph is a good account of the disease. Triller's thesis may be recommended, but it contains some errors. The contribution of Nicolas and Jambon is among the best of the many modern French articles which take the broad view that pellagra is really not a morbid entity.

ITALIAN.

STRAMBIO, G. *Dissertazioni sulla pellagra*. Vols. I and II, Milano, 1794. Also *Lettere ad un amico*, 1822.

LUSSANA, F., and FRUA, C. *Su la pellagra*. Milano, 1856.

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ANTONINI, G. *La pellagra*. Milano, 1902.

GOSIO, B. *Sul problema etiologico della pellagra*. *Atti del Terzo Cong. Pel. Ital.* Udine, 1907.

ALESSANDRINI, G. *Sulla pellagra in Italia*. *Annali d' Igiene Sper.*, n. s., XX, fasc. IV. Also reprint.

Rivista Pellagologica Italiana. (A bimonthly journal devoted exclusively to pellagra. Its files extend from 1901.)

Atti del Congresso Pellagologico Italiano, I-IV. (These congresses were held in 1901, 1902, 1907, and 1909. There is a volume of transactions for each congress.)

There is such a wealth of Italian literature that selection is very difficult. The files of the *Rivista Pellagologica Italiana* and the *Transactions of the National Congresses* will put the reader in touch with all of the modern literature. Of the references given above Strambio's *Dissertations* are interesting and instructive. This is the elder Strambio, one of the first great writers on the disease. This family for three generations have been students of pellagra. Lombroso's writings are voluminous; the reference given is to his last important work. The article by Belmonto is a discussion of typhoid pellagra. Antonini's manual is a small handbook and gives a good general account. He has written many other things. Gosio's article gives a good study of the etiology. He is the author of many other articles and may be classed as one of the sanest of the zeist writers on etiology. Alessandrini's article is an epidemiologic study made in support of his hypothesis. It contains many new facts.

ENGLISH.

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MANSON, Sir P. *Pellagra*. In his *Tropical Diseases*, fourth edition, London and New York, 1907.

SCHEUBE, B. *Pellagra*. In his *Diseases of Warm Countries*, edited by Cantlie. Philadelphia, 1902.

SAMBON, L. W. *Progress report on the investigation of pellagra*. *Journal of Tropical Medicine and Hygiene*, XIII, 18, 19, 20, and 21, 1910.

The British literature is not very extensive. Sandwich has written of pellagra in Egypt and has directed attention to the gravity of the disease in that country. The article in Allbutt's *System* is not long. The article in Manson's book is very good, but is not an unbiased treatment of the subject. The article



SOUTH CAROLINA CASE.—ERYTHEMA OF FACE, HANDS, FOREARMS, AND UPPER CHEST. NOTE THE PECULIAR DISTRIBUTION ON THE FACE.

Courtesy of Dr. J. W. Babcock, Physician and Superintendent State Hospital for Insane, Columbia, S. C.

by Scheube is an excellent one and gives a bibliography. Sambon's report is an epidemiologic study of the disease in Italy, made in support of his hypothesis. It contains many new and interesting observations. There has recently been advertised a more extensive treatise along the same lines by Sambon.

The American literature will be found largely in the journals since 1907. Excellent contributions have been made by Harris, Searcy, Babcock, Watson, Wood, Bellamy, Taylor, McCampbell, King, Randolph, Alsberg, Bass, Bondurant, Cole, Siler, Nichols, Zeller, Saunders, Dyer, Pollock, Hyde, Long, Thayer, Anderson, and many others. There have been several official publications by the Public Health and Marine-Hospital Service; also the publication, as a Senate document, of Cutting's consular report. The transactions of the two conferences on pellagra held at Columbia, S. C., in 1908 and 1909 contain many articles. Reference has already been made to the translation of Marie's monograph. Some of the State Boards of Health have published bulletins on the disease, notably in South Carolina and Illinois.

LIST OF PUBLIC HEALTH BULLETINS.

The following is a list of the Public Health Bulletins that have been issued:

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- *2. Report on the Etiology and Prevention of Yellow Fever. By George M. Sternberg. 1890. 271 pages. 21 pl. 20 il. Cloth. Out of print.
- *3. Mortality Statistics in the United States for the year ending December 31, 1897. From Annual Report Marine-Hospital Service, 1898. 24 pages. Paper. Out of print.
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- *14. Sanatorium for Consumptives, Fort Stanton, N. Mex. By P. M. Carrington, Reprint from Annual Report Public Health and Marine-Hospital Service, 1904. 19 pages. Paper. Out of print.
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- 16. How to Prevent Yellow Fever—No Mosquitoes. No Yellow Fever. By Walter Wyman. July 31, 1905. 3 pages. Circular.
- 17. Transactions of the Fourth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. May, 1906. 75 pages. Cloth.
- 18. Transactions of the Fifth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. May, 1907. 47 pages. Cloth.
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TREASURY DEPARTMENT

Public Health and Marine-Hospital Service of the United States

PUBLIC HEALTH BULLETIN No. 49

OCTOBER, 1911

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AN ANALYSIS OF THE LAWS AND REGULATIONS
RELATING THERETO IN FORCE IN
THE UNITED STATES

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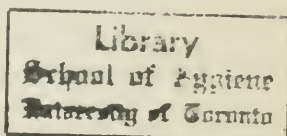
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OPHTHALMIA NEONATORUM.

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THE UNITED STATES.

By J. W. KERR, *Assistant Surgeon General.*

The undue prevalence of ophthalmia neonatorum and its dire effects on the individual forces upon sanitarians and social workers the great importance of prophylaxis. The disease and its methods of transmission have long been known, and it is recognized that it is easily preventable. Notwithstanding this fact, it is generally estimated that from 25 per cent to 40 per cent of all blindness can be referred to this cause.

There are no complete statistics showing the prevalence of ophthalmia neonatorum, and only an approximate idea can be had of the number of cases by studying the admissions to schools for the blind. A committee of the British Medical Association found that more than one-third of those in blind schools of Great Britain owed their affliction to this disease.¹

In the United States and Canada in 1907, out of 224 admissions to 10 schools for the blind, 59, or 24.38 per cent, were blind as a result of ophthalmia neonatorum;² and out of 351 admissions to certain schools in the United States and Canada in 1910, 84, or 23.9 per cent, were blind from this cause.³

As a result of studies made of ophthalmia neonatorum in 10 manufacturing cities of Massachusetts, Greene has presented figures which show that the minimum morbidity rate for this disease was 6.4 per 1,000 births. A more complete census made by him for the practice of 173 physicians in 9 cities revealed an average morbidity rate of 10.8 per 1,000 births.⁴

These ratios, of course, only apply to the localities in which the investigations were made. The statistics presented here and elsewhere, however, and the experience of the medical profession, are sufficient to emphasize the importance of the disease and to indicate that its continued prevalence is a matter of serious concern.

When it is realized that the exercise of practically all of the trades or professions open to man depends almost absolutely on good eye-

¹ British Medical Journal, May 8, 1909.

² Journal, American Medical Association, May 23, 1909, p. 1745.

³ Journal, American Medical Association, July 1, 1911, p. 72.

⁴ Monograph Series of the American Association for Conservation of Vision, Vol. 1, No. 1.

sight, the importance of ophthalmia neonatorum as an economic factor becomes evident. Every child infected with the disease, if left untreated, eventually may become dependent upon the community for his support. His education will be more expensive, his power to earn a livelihood will be permanently impaired, and instead of becoming a useful member of society, he may, and through no fault of his, become a permanent public charge.

In the United States, the State of Massachusetts appropriated \$40,000 in 1910 for the support of its blind asylums; the State of New York, \$110,000; while the biennial appropriation for the State of Pennsylvania for its institutions of the same kind in 1909 amounted to \$265,000. When we aggregate private expenses, amounts spent by States and cities, and also the estimate of the potential earning power of individuals thus disabled, the economic loss on account of ophthalmia neonatorum is enormous.

LEGISLATIVE MEASURES FOR THE CONTROL OF OPHTHALMIA NEONATORUM.

Notwithstanding this great economic loss to the State on account of ophthalmia neonatorum, it was not until 1881 that Credé gave to the world a prophylactic, thereby connecting forever his name with the prevention of the disease and the subsequent saving of the sight of infants. The effective and simple way in which he checked the infection by the use of silver salts, and the statistics compiled by him and others, gave substantial support to his theories, which have been gradually incorporated in the sanitary policy of all civilized countries. Legislative bodies both in this country and abroad having accordingly had impressed upon them the importance of the disease have adopted various legal measures for its control.

It is the object of this bulletin to present a comparative statement of the several measures adopted in the different States and to bring together copies of the laws in which they are contained. Brief mention is also made of measures that are required to be taken in certain countries abroad.

SOME MEASURES REQUIRED TO BE OBSERVED ABROAD.

In France ophthalmia neonatorum is classed as one of the communicable diseases, must be reported, and is subject to disinfection. In Italy the regulations for midwives provide that the lids and conjunctivæ of infants must be washed after birth with a disinfecting solution, and that if an inflammation develops a physician must be called immediately.

In Belgium a physician must be called to attend all cases of ophthalmia neonatorum, while midwives, before bathing the infant, are required to wash its eyes with sterilized water. In Bavaria the midwife is required to carry with her a vial containing the nitrate

of silver solution with directions for its use. In Austria a penalty is provided for midwives failing to call a doctor in cases of ophthalmia neonatorum. Similar regulations are in force in Switzerland.

The Ophthalmic Society of Great Britain and Ireland has recommended that the following note be printed on all birth certificate forms: "If the eyelids are red and swollen, or form the site of a secretion some days after birth, the child should be taken to the physician without delaying one day. The disease is very dangerous; if not cured in time the sight of both eyes may be lost." The insertion of a similar statement in the birth certificates used in the different States would no doubt be productive of much good, and some benefit might also be expected from reserving in the certificate a space for the reporting of the condition of the eyes.

LEGISLATION IN THE UNITED STATES.

So far as known, the first legal steps taken by any State to control ophthalmia neonatorum in the United States were those of Maine in 1891, when its legislature enacted the first law relative to ophthalmia neonatorum in this country. In 1892 New York followed with an amendment to the law relative to midwives and nurses.

Subsequently, other States took legislative action. The dates of the respective laws are as follows:

Maine	Mar. 28, 1891
New York	Apr. 18, 1892
Rhode Island	Apr. 19, 1892
Minnesota	¹ Feb. 22, 1893
Ohio	Mar. 16, 1894
Maryland	Apr. 6, 1894
New Jersey	Mar. 11, 1895
Michigan	Mar. 29, 1895
Missouri	Apr. 3, 1895
Connecticut	Apr. 18, 1895
Illinois	June 21, 1895
Pennsylvania	June 26, 1895
South Carolina	Feb. 25, 1896
Iowa	Apr. 3, 1896
Porto Rico	Oct. 24, 1899
Massachusetts	Mar. 31, 1905
Idaho	Mar. 12, 1907
Wisconsin	Apr. 21, 1909
Vermont	Nov. 11, 1910
Tennessee	Feb. 13, 1911
Indiana	Mar. 4, 1911
North Dakota	Mar. 6, 1911
Utah	Mar. 9, 1911
Texas	² Mar. 23, 1911
New Hampshire	Apr. 12, 1911

¹ Repealed by chap. 108 Revised laws, 1905. Provisions now incorporated in regulations.

² Since Jan. 4, 1910, a provision of the sanitary code.

In addition to the above States, provisions with respect to ophthalmia neonatorum are contained in the Sanitary Code of Louisiana. Nebraska has incorporated in the regulations of the State board of health various recommendations regarding the disease, and the Kansas State Board of Health has recommended and the Oregon State Board and New York Department of Health require its being reported by physicians. In the District of Columbia also regulations became effective August 25, 1911, requiring midwives or persons other than physicians in charge of cases of childbirth to report within six hours the occurrence of inflammation of the eyes of the new-born when attended by discharge.

The provisions of the several laws are quite varied. In all of them, however, it is the object to insure early treatment of cases of ophthalmia neonatorum, and to this end reports in some form or another are required to be made of the occurrence of cases in all the States mentioned, except Nebraska.¹

It will be understood that in the majority of the States such cases are not required to be reported in the manner prescribed for other communicable diseases. In some States these reports are required to be made by the parents; in others, by midwives, nurses, or guardians; and in still others, by physicians in attendance. In South Carolina, the law requiring reports does not apply to towns under 1,000 inhabitants. The cases must be reported within six hours in Connecticut, Idaho, Illinois, Indiana, Iowa, Massachusetts, New Jersey, Ohio, Pennsylvania, Rhode Island, Utah, and Wisconsin; within 12 hours in Louisiana, Minnesota, Porto Rico, and Texas; and immediately in Kansas, Maine, Maryland, Michigan, Missouri, New York, South Carolina, and Tennessee.

These reports must be made to local health authorities in Connecticut, Louisiana, Indiana, Massachusetts, Minnesota, New Jersey, North Dakota, South Carolina, Utah, Vermont, Wisconsin; to either the health authorities or a medical practitioner in Idaho, Illinois, Iowa, Maryland, Michigan, New York, Ohio, Rhode Island, Pennsylvania, Tennessee, Texas; and only to a medical practitioner in Maine, Missouri, and Porto Rico.

The disease must be reported by the midwife, nurse, or attendant in all these States. In addition, the laws of Indiana, Massachusetts, North Dakota, and Utah specifically state that cases must be reported by physicians, and the same provision is contained in the regulations of the State health authorities of Kansas, Oregon, and New York.

In Indiana and North Dakota, provision is made in law whereby all birth certificates shall have thereon the question "Were precautions taken against ophthalmia neonatorum?" and failure to answer

¹ Pub. Health Bull. No. 45, P. II. and M. H. S.: A Digest of Laws and Regulations of the Various States Relating to the Reporting of Sickness.

the same renders unlawful all bills or charges for professional services in connection with the case.

Other States as Minnesota, New York, and Ohio have a similar requirement in their birth certificates. The following is the form of certificate used in New York:

PLACE OF BIRTH.		NEW YORK STATE DEPARTMENT OF HEALTH, BUREAU OF VITAL STATISTICS.	
County of		CERTIFICATE OF BIRTH.	
Town of		Registered No.	
or Village of		(No., ... St. ward.)	
or City of			
Full name of child		(If child is not yet named, make supplemental report, as directed.)	
Sex of child.	Twin, triplet, or other? (To be answered only in event of plural births.)	Number in order of birth.	Legitimate? Date of birth 19.... (Month.) (Day.) (Year.)
FATHER.		MOTHER.	
Full name		Full maiden name	
Residence		Residence	
Color or race..... Age at last birthday..... (Years.)		Color or race..... Age at last birthday..... (Years.)	
Birthplace.....		Birthplace.....	
Occupation.....		Occupation.....	
What preventive for ophthalmia neonatorum did you use?.....		Number of children born to this mother, including present birth.....	
If none, state the reason therefor.....		Number of children of this mother now living.....	

CERTIFICATE OF ATTENDING PHYSICIAN OR MIDWIFE.¹

I hereby certify that I attended the birth of this child, who was born alive at M., on the date above stated.

	(Signature)
	Dated 19.... (Physician, midwife, father, etc.)
Given name added from a supplemental report..... 19....	Address
	Filed 19....
Registrar.	Registrar.

The provisions of the laws confine themselves merely to requiring reports of cases in Connecticut, Idaho, Illinois, Maine, Maryland, Michigan, Missouri, Ohio, Rhode Island, South Carolina, Tennessee, and Texas. Health authorities must, when no physician is in charge, furnish remedial treatment in Indiana, Louisiana, Minnesota, New Jersey, and Wisconsin.

The State health authorities of Massachusetts, New Jersey, and Vermont are specifically authorized in law to furnish prophylactic outfits to physicians for use in their practice. Rhode Island was the first State, however, to introduce such outfits, which are distributed through diphtheria antitoxin stations and under general authority vested in the State board of health for the preservation of the public health. In New York also provision is made for the control and prevention of ophthalmia neonatorum, and in accordance therewith

¹ When there was no attending physician or midwife, then the father, householder, etc., should make this return.

prophylactic packets are given away through health officers. In the District of Columbia similar packets are issued to midwives by the health department.

The outfit distributed by the State health authorities ordinarily consists of a small vial holding an amount of a 1 per cent solution of nitrate of silver sufficient for use on a child, a sterilized dropper and bulb, and a circular containing instructions for administration.

The treatment must be conducted in accordance with the rules of the State board of health in Utah, Vermont, New Hampshire, and Wisconsin. The treatment to be followed is prescribed in the law of Porto Rico and the health regulations of Nebraska. Local health authorities must instruct parents as to the dangers of the disease in Pennsylvania and Wisconsin, and physicians and midwives must do likewise in Iowa and physicians and nurses in Nebraska. Copies of the law must be furnished by local health authorities to midwives and nurses in Missouri, New Jersey (also to medical practitioners), Pennsylvania, and Rhode Island. Disinfection of clothing is required in both Nebraska and Porto Rico.

Authority is specifically conferred by law on the State board of health of Wisconsin to distribute literature relative to the disease, and in the use of their general powers such literature has been issued during 1910 by the State health authorities of California, Indiana, Kansas, Kentucky, Maryland, Massachusetts, New Jersey, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Tennessee, Vermont, and Wisconsin.

All of the laws in force contain one or more good provisions, such as those requiring birth reports, with reference or instructions in them regarding ophthalmia neonatorum; case reports to health authorities not only by midwives but also by physicians and parents; distribution of literature; instructions as to treatment; disinfection; furnishing of prophylactics; control over midwives; and medical attendance if the person is unable to pay. All of these provisions would be included in a uniform law, which is desirable in order to successfully control ophthalmia neonatorum.

Unfortunately the activities of the sanitarian are too often restrained to pointing out the evils of ophthalmia neonatorum with no means at his disposal to combat them. It is society as a whole, in the last analysis, which must utilize the knowledge at its disposal and furnish the means to eliminate the disease. These are cheap and comparatively easy of application, but society must ultimately decide whether it is willing to pay the price.

STATE LAWS AND REGULATIONS RELATING TO OPHTHALMIA NEONATORUM.

The following laws were compiled in the bureau from the statutes of the several States and Territories, as found in the Law Library of Congress, and from copies of recent laws transmitted by special request by the respective State health authorities.

Galley proof of the analysis of the laws, and the laws themselves, were submitted to the health officials of the several States and Territories for criticism and correction, and acknowledgment is due and here made for this service and for helpful suggestions.

CONNECTICUT.

(General Statutes, 1902.)

Sec. 2535. Should one or both eyes of an infant become inflamed or swollen, or reddened at any time within two weeks after its birth, the midwife, nurse, or attendant having charge of such infant shall report in writing, within six hours, to the health officer or board of health of the city, town, or borough in which the parents of the infant reside, the fact that such inflammation, swelling, or redness of the eyes exists. Every person violating the provisions of this section shall be fined not more than \$200.

DISTRICT OF COLUMBIA.

(Regulations for the prevention of infant blindness.)

SECTION 1. Whenever any midwife, or any person other than a registered physician, is in attendance upon any case of childbirth and the newly born child has inflammation of the eyes, attended by a discharge therefrom, said midwife or other person shall report that fact in writing to the health officer, so that said report shall be received by the health officer within the six hours after the existence of said discharge becomes known to said midwife.

SEC. 2. No midwife or person other than a registered physician shall treat any case of inflammation of the eyes of a newly born child attended by a discharge therefrom for any period longer than may be absolutely necessary to obtain the services of a registered physician.

SEC. 3. Any person who violates any of the provisions of these regulations shall, upon conviction thereof in the police court, be punished by a fine not exceeding \$40. Prosecutions for violations of the provisions of these regulations shall be on information filed in the police court by the Corporation Counsel of the District of Columbia or by any of his assistants.

IDAHO.

(Revised Codes, 1908.)

SEC. 1108. Should one or both eyes of an infant become inflamed or swollen or reddened, or should any pus or secretion form in the eyes or upon the edge of the lid, at any time within two weeks after birth, it shall be the duty of any midwife, nurse or other person having charge of such infant to report, within six hours after discovery

of such inflammation, redness or formation of pus or secretion, to the local health officers, or to some legally qualified practitioner of medicine in the district in which such case shall occur, the fact that such inflammation, swelling or redness or accumulation in the eye exists. Any failure to comply with the provisions of this section shall be punished by a fine of not to exceed one hundred dollars, or imprisonment not to exceed ninety days, or by both fine and imprisonment, in the discretion of the court.

ILLINOIS.

(Chapter 38, Hurd's Revised Statutes, 1909.)

SEC. 510. Should any midwife or nurse having charge of an infant in this State, notice that one or both eyes of such infant are inflamed or reddened at any time within two weeks after its birth, it shall be the duty of such midwife or nurse having charge of such infant to report the fact in writing within six (6) hours to the health officer, or some legally qualified practitioner of medicine of the city, town, or district in which the parents of the infant reside.

SEC. 511. Any failure to comply with the provisions of this act shall be punishable by a fine not to exceed one hundred (\$100) dollars, or imprisonment not to exceed six (6) months, or both.

INDIANA.

(Acts of 1911, chapter 129.)

SECTION 1. Whenever a child is born, the physician, midwife or any other person who is present and engaged as professional attendant, shall report said birth on a blank supplied by the State board of health to the health officer having jurisdiction, within 36 hours after such birth occurs. Said birth certificate in addition to other data ordered by the State board of health shall have upon it this question: Were precautions taken against ophthalmia neonatorum? And it shall be a violation of this act for any physician or midwife in professional attendance at a birth to fail to report same as herein commanded or to omit answering the said question: Were precautions taken against ophthalmia neonatorum? All bills or charges for professional services rendered at a birth shall be unlawful if report is not made as herein commanded.

SEC. 2. It shall be the duty of all physicians or midwives in professional attendance upon a birth to always carefully examine the eyes of the infant, and if there is the least reason for suspecting infection of one or both eyes then said physician or midwife in professional attendance shall apply such prophylactic treatment as may be recognized as efficient in medical science.

SEC. 3. Should one or both eyes of an infant become inflamed, swollen, or reddened, or show any unnatural discharge or secretion at any time within two weeks after its birth, and no legally qualified physician is in attendance upon the infant at that time, it shall be the duty of its parents, or in their absence, whoever is caring for said infant to report the fact in writing within six hours after discovery to the health officer having jurisdiction: *Provided*, Said report to said health officer need not be made from recognized hospitals.

SEC. 4. Upon receipt of a report as set forth in section 3 of this act health officers shall direct the parents, or whoever has charge of such infant suffering from such inflammation, swelling, redness or unnatural secretion or discharge of the eyes, to immediately place it in charge of a legally qualified physician or in charge of the city or township physician if unable to pay for medical service.

SEC. 5. Any violation of the provisions of this act shall be punished by a fine of not less than ten dollars nor more than fifty dollars.

IOWA.

(Acts of 1896, chapter 57.¹)

SECTION 1. Should one or both eyes of an infant become inflamed, or swollen, or reddened at any time within two weeks after its birth, it shall be the duty of the midwife, parent, guardian, or nurse, or other persons having charge of such infant to report within six (6) hours after the discovery thereof by such person in charge of such infant to the health officer or some legally qualified practitioner of the city, town, or district in which the parents of the infant reside, the fact that such inflammation, or swelling, or redness of the eyes exists.

SEC. 2. It is hereby made the duty of attending physicians or midwives to instruct parents and nurses in regard to the provisions of this act and danger of sore eyes in infants.

SEC. 3. Any failure to comply with the provisions of this act shall be punished by a fine not less than twenty-five dollars or more than one hundred dollars, or imprisonment in the county jail not to exceed 30 days or both.

KANSAS.

(Resolution, State board of health.)

That * * * ophthalmia neonatorum be included in the diseases required to be reported by the attending physician.

LOUISIANA.

(Sanitary Code, 1911.)

62. (a) Whenever in any community of this State, any nurse, midwife or other person not a legally qualified practitioner of medicine shall notice inflammation of the eyes or redness of the lids in a newborn child under his or her care, it shall be the duty of such person to report the same to the town or parish health officer within 12 hours of the time the disease is first noticed.

(b) Upon such notification it shall be the duty of the municipal or parish health officer to serve notice on the family to inform their family physician.

(c) Where no physician is in attendance, or where by reason of the inability of the family to employ a physician, it will be his duty to provide remedial relief at the expense of the municipality, or at the expense of the parish if the afflicted lives without the corporate limits of any municipality.

MAINE.

(Revised Statutes, 1903, chapter 18.)

SEC. 90. If one or both eyes of an infant become reddened or inflamed at any time within four weeks after birth, the midwife, nurse or person having charge of said infant shall report the condition of the eyes at once to some legally qualified practitioner of medicine of the city, town or district in which the parents of the infant reside. Any failure to comply with the provisions of this section shall be punishable by a fine not to exceed one hundred dollars, or imprisonment not to exceed six months.

MARYLAND.

(Code of 1904, article 27.)

SEC. 231. If at any time within two weeks after the birth of any infant one or both of its eyes, or the eyelids, be reddened, inflamed, swollen or discharging pus, the midwife, nurse or person other than a legally qualified physician in charge of such infant shall refrain from the application of any remedy for the same, and shall

¹ Omitted from Code of 1897. Sec. 27, chap. 29, acts of 1897 declares that the code is "the authoritative publication of the existing laws of the State."

immediately report such condition to the health commissioner or to some legally qualified physician in the city, county or town wherein the infant is cared for. Any person and persons violating the provisions of this act shall, on conviction, be punished by a fine not to exceed one hundred dollars, or by imprisonment in jail not to exceed six months, or by both fine and imprisonment.

MASSACHUSETTS.

(Revised Laws, 1902, chapter 75.)

SEC. 49 (as amended by chap. 269, acts of 1910). * * * Should one or both eyes of an infant become inflamed, swollen and red, and show an unnatural discharge at any time within two weeks after its birth, it shall be the duty of the nurse, relative or other attendant having charge of such infant to report in writing within six hours thereafter, to the board of health of the city or town in which the parents of the infant reside, the fact that such inflammation, swelling and redness of the eyes and unnatural discharge exist. On receipt of such report, or of notice of the same symptoms given by a physician as provided by the following section, the board of health shall take such immediate action as it may deem necessary in order that blindness may be prevented. Whoever violates the provisions of this section shall be punished by a fine of not more than one hundred dollars * * *.

SEC. 50 (as amended by chap. 480, acts of 1907). * * * If one or both eyes of an infant whom or whose mother he (a physician) is called to visit become inflamed, swollen and red, and show an unnatural discharge within two weeks after the birth of such infant, he shall immediately give notice thereof in writing over his own signature to the selectmen or board of health of the town: and if he refuses or neglects to give such notice, he shall forfeit not less than fifty nor more than two hundred dollars for each offense.

(Chapter 458, acts of 1910.)

SEC. 1. The State board of health shall furnish, free of cost, to physicians registered under the laws of the Commonwealth such prophylactic remedy as it may deem best for the prevention of ophthalmia neonatorum

SEC. 2. To carry out the provisions of this act there may be expended annually from the treasury of the Commonwealth a sum not exceeding twenty-five hundred dollars.

(Acts of 1911, chapter 643.)

The sums hereafter mentioned are appropriated * * * for the salaries and expenses of the State board of health for the fiscal year ending on the 30th day of November, 1911, to wit:

For expenses in carrying out the provisions of the law relative to the prevention of ophthalmia neonatorum,¹ a sum not exceeding two thousand five hundred dollars.

MICHIGAN.

(Compiled Laws of 1897.)

SEC. 4475. Should one or both eyes of an infant become inflamed or swollen, or reddened, or should any pus or secretion form in the eyes or upon the edge of the lids, at any time within two weeks after birth, it shall be the duty of any midwife, nurse or other person having charge of such infant, to report in writing within six hours after discovery of such inflammation, redness or formation of pus, or secretion, to the local health officer or some legally qualified practitioner of medicine in the

¹ Ophthalmia neonatorum made also notifiable by resolution of the State board of health on May 6, 1909

city, town or district in which such case shall occur, the fact that such inflammation, swelling or redness or accumulation in the eyes exists.

SEC. 4476. Any failure to comply with the provisions of this act shall be punished by a fine not to exceed one hundred dollars or imprisonment not to exceed six months, or both such fine and imprisonment in the discretion of the court.

MINNESOTA.

(Regulations, State board of health.)

SEC. 80. Whenever one or both eyes of an infant become inflamed, reddened or diseased at any time within two months after its birth, it shall be the duty of any midwife, nurse, parent or other person having charge of such infant to report the facts of such affection in writing to the local health officer of the city, village or township in which the person having charge of said infant resides within 12 hours after ascertaining the fact.

SEC. 81. Any health officer to whom may have been reported any case of eye disease in a child under two months of age shall forthwith visit said child and provide immediate medical treatment unless said child is already under the charge of a competent medical practitioner.

MISSOURI.

(Revised Statutes, 1909.)

SEC. 8321. Should one or both lids of either eye or of both eyes of an infant become red or swollen, or should there be any discharge from either eye or from both eyes, at any time within three weeks after its birth, it shall be the duty of the midwife, nurse or other person having charge of said infant, at once, unless for good cause shown, to report the condition of said eyes to a legally qualified practitioner of medicine.

SEC. 8322. Every health officer shall furnish a copy of sections 8321 to 8323, inclusive, to each and every person who is known to him to act as midwife or nurse in the city or town from which such health officer is appointed, and the secretary of state shall cause a sufficient number of copies of said sections to be printed and shall supply the same to the health officers on application.

SEC. 8323. Any failure to comply with said provisions of sections 8321 and 8322 shall be a misdemeanor, and shall be punishable by a fine of not less than ten nor more than one hundred dollars, or by imprisonment not to exceed six months, or by both such fine and imprisonment.

NEBRASKA.

[Regulations, State board of health.]

RULE 29. The disease ophthalmia neonatorum, prevalent only among newborn infants, is one of the most fruitful sources of blindness. All things considered, where there is the least suspicion of the prevalence of any gonorrhœal infection, or a mucopurulent discharge from the vagina during birth the attending physician shall take precautionary measures at once to prevent this fearful disease. This consists in the instillation of two drops of a 2 per cent solution of nitrate of silver in the eyes of the newborn child after thoroughly cleansing the eyelids, then parting them and introducing the drug. When there is reason to suspect gonorrhœal contagion this must be repeated the second day. * * * It is the duty of physicians, nurses and directors of public charities to disseminate among the poorer classes a knowledge of the dangers of this disease and the necessity for prompt treatment. Disinfection of the clothing of the patient, and burning of all cloths, etc., is essential, as there is great danger of contamination.

NEW HAMPSHIRE.

[Acts of 1911, chap. 121.]

SECTION 1. The State board of health is hereby vested with power and authority to publish such information and instruction and to make such rules, regulations and ordinances as it may deem expedient to prevent the development of inflammation of the eyes of the newborn babe, or so-called ophthalmia neonatorum, in public hospitals or institutions in which midwifery is practiced, either wholly or in part, and in connection with the practice of legally licensed midwives.

SEC. 2. Said State board of health is authorized to enforce its rules, regulations and ordinances through its inspectors, or through the local boards of health.

SEC. 3. Any person violating [any rule, regulation or ordinance of said State board of health regarding the prevention of ophthalmia neonatorum shall be guilty of a misdemeanor.

NEW JERSEY.

[General statutes, 1895, p. 1676.]

SECTION 1. Should one or both eyes of an infant become inflamed, swollen, or reddened, or show any unnatural discharge at any time within two weeks after its birth, and no legally-qualified practitioner of medicine be in attendance upon the infant at the time, it shall be the duty of the midwife, nurse, attendant, or relative having charge of such infant to report the fact in writing, within six hours, to the local board of health of the city, township, or other municipality in which the parents of the infant reside.

SEC. 2. The said local board of health shall direct the parents or person having charge of such infant suffering from such inflammation, swelling, redness, or unnatural discharge of the eyes to immediately place it in charge of a legally-qualified practitioner of medicine, or in charge of the physician of the city, township, or other municipality if unable to pay for medical services.

SEC. 3. (As amended by chap. 147, acts of 1910.) Every local board of health in the State of New Jersey shall furnish a copy of this act to every legally-qualified practitioner of medicine, and to each person who is known to act as a midwife or nurse in the city, township, or other municipality for which such board of health is appointed; and the board of health of the State of New Jersey shall cause a sufficient number of copies of this act to be printed and supply the same to each local board of health of this State for distribution.

SEC. 4. (As amended by chap. 147, acts of 1910.) Any person violating any of the provisions of this act shall be liable to a penalty of \$50, to be recovered in an action of debt by the local board of health of the municipality in which the violation occurs.

[Acts of 1911, chap. 96.]

SECTION 1. The State board of health shall furnish, free of cost, to physicians and midwives, registered under the laws of this State, such prophylactic remedies as it may deem best for the prevention of ophthalmia neonatorum, together with such instructions as it may deem necessary for the proper administration of the same.

SEC. 2. The sum of \$2,000 is hereby appropriated for the purpose of carrying out the provisions of this act when included in the annual or supplemental appropriation bill.

NEW YORK.

(Consolidated Laws, 1909, chap. 40.)

SEC. 482. A person who: * * * 3. Being a midwife, nurse or other person having the care of an infant within the age of two weeks neglects or omits to report immediately to the health officer or to a legally qualified practitioner of medicine of the city, town or place where such child is being cared for, the fact that one or both

eyes of such infant are inflamed or reddened, whenever such shall be the case, or who applies any remedy therefor without the advice, or except by the direction of such officer or physician; * * * is guilty of a misdemeanor.

(Acts of 1910, chapter 513.)

SEC. 1. The treasurer shall pay * * * to the persons, and for the purposes indicated in this act, the amount named or so much thereof as shall be sufficient to accomplish, in full, the purposes designated by the appropriations (p. 1141).

(Health department.)

For the control and prevention of ophthalmia neonatorum and the prevention of blindness, five thousand dollars (\$5,000), or as much thereof as may be necessary.

State department of health, Public Health Manual (p. 129).

Every physician is required by law to report at once all cases of communicable disease in his care to the health officer, and if no physician is in attendance, the duty is imposed on the householder where the case occurs.

The diseases to be so reported have, under the law, been designated by the State commissioner of health as * * * ophthalmia neonatorum * * *.

The occurrence of these diseases should be reported immediately to the State department of health by the health officer * * *.

NORTH DAKOTA.

(Acts of 1911, chap. 188.)

SECTION 1. Whenever a child is born, the physician, midwife or any other person who is present and engaged as professional attendant, shall report said birth on a blank supplied by the State board of health to the health officer having jurisdiction, within 36 hours after such birth occurs. Said birth certificate in addition to other data ordered by the State board of health shall have upon it this question: "Were precautions taken against ophthalmia neonatorum?" And it shall be a violation of this act for any physician or midwife in professional attendance at a birth to fail to report same as herein commanded or to omit answering the said question, "Were precautions taken against ophthalmia neonatorum?" All bills or charges for professional services rendered at a birth shall be unlawful if report is not made as herein commanded.

SEC. 2. It shall be the duty of all physicians or midwives in professional attendance upon a birth to always carefully examine the eyes of the infant, and if there is the least reason for suspecting of disease of the eyes then said physician or midwife in professional attendance shall apply such prophylactic treatment as may be recognized as efficient in medical science.

SEC. 3. Should one or both eyes of an infant become inflamed, swollen or reddened, or show any unnatural discharge or secretion at any time within two weeks after its birth, and no legally qualified physician is in attendance upon the infant at that time, it shall be the duty of its parents or, in their absence, whoever is caring for said infant to report the fact in writing within six hours after discovery to the health officer having jurisdiction. *Provided*, Said report to said health officer need not be made from recognized hospitals.

SEC. 4. Upon receipt of a report as set forth in section 3 of this act, health officers shall direct the parents or whoever has charge of such infant suffering from such inflammation, swelling, redness or unnatural secretion or discharge of the eyes, to immediately place it in charge of a legally qualified physician, or in charge of the city or township physician if unable to pay for medical services.

SEC. 5. Any violation of the provisions of this act shall be punished by a fine of not less than ten dollars nor more than fifty dollars.

OHIO.

(General Code, 1910.)

SEC. 12787. *Failure to report infant with diseased eyes.*—Whoever, being a midwife, nurse or relative in charge of an infant less than 10 days old, fails within six hours after the appearance thereof to report in writing to the physician in attendance upon the family, or if there be no such physician, to a health officer of the city, village or township in which such infant is living, or, in case there be no such officer, to a practitioner of medicine legally qualified to practice, that such infant's eye is inflamed or swollen or shows an unnatural discharge, if that be the fact, shall be fined not less than five dollars nor more than one hundred dollars or imprisoned not less than thirty days nor more than six months, or both.

OREGON.

(Rules and regulations, State board of health, 1911.)

Rule 1. It shall be the duty of every practicing physician in the State of Oregon to report to the county health officer, or to the health officer of the municipal corporation, * * * within 24 hours, by the quickest means of communication, * * * all cases of * * * ophthalmia neonatorum * * * within his jurisdiction.

Rule 3. It shall be the duty of the superintendent of any State institution, and of the superintendent of any children's home or any other institution of public nature, to report to the secretary of the State board of health any of the diseases named in rule 1 * * *.

PENNSYLVANIA.

(Purdon's Digest, 13th edition, p. 1886.)

SEC. 78. Should one or both eyes of an infant become inflamed or swollen or reddened at any time within two weeks after birth, it shall be the duty of the midwife or nurse, or other person having the care of such infant, to report in writing, within six hours after the discovery thereof, to the health officer or legally qualified practitioner of the city, town or district in which the mother of the child resides, the fact that such inflammation or swelling or redness exists.

SEC. 79. It shall be the duty of said health officer, immediately upon receipt of said written report, to notify the parents or the person having charge of said infant, of the danger to the eye or eyes of said infant by reason of said condition from neglect of proper treatment of the same, and he shall also inclose to them directions for the proper treatment thereof.

SEC. 80. Every health officer shall furnish a copy of this act to each person who is known to him to act as midwife or nurse in the city or town for which such health officer is appointed, and the secretary of state shall cause a sufficient number of copies of this act to be printed and supply the same to such health officers on application.

SEC. 81. Any failure to comply with the provisions of this act shall be punishable by fine not to exceed two hundred dollars or imprisonment not to exceed thirty days, or both.

(Acts of 1911, page 931.)

SEC. 10. If at any time within two weeks after the birth of an infant, one or both of its eyes or the eyelids be reddened, inflamed, swollen, or discharging pus, the midwife, nurse, or person, other than a legally qualified physician, in charge of such infant, shall refrain from the application of any remedy for the same, and shall immediately report such condition to the local health authorities, and, at the same time, to some legally qualified physician in the city, town, or county wherein the infant is cared for. Any person or persons violating the provisions of this section shall, on conviction, be punished by a fine not to exceed one hundred dollars, or by imprisonment in jail not to exceed six months, or by both fine and imprisonment, in the discretion of the court, alderman, magistrate, or justice of the peace.

(General Order No. 170, 1899.)¹

SEC. 51. Thirty per cent or more of existing blindness has been shown to be due to infection of the eyes at or shortly after birth. This infection being readily amenable to treatment, it is ordered that whenever in any city, district or place in this island any nurse, midwife, or other person, not a legally qualified practitioner of medicine, shall notice any inflammation of the eyes or redness of the lids in a newborn child under his or her care, it shall be the duty of such person to report the same to some legally qualified practitioner of medicine within twelve hours of the time the disease is first noticed.

SEC. 52. It shall be the duty of every legally qualified practitioner of medicine to treat all cases of "ophthalmia neonatorum" by the Credé method, which is as follows:

SEC. 53. Gently open the lids and wash out the eyes with pure lukewarm water, which has been boiled, using a clean soft piece of old linen or muslin or a pledget of absorbent cotton, but do not use a sponge.

SEC. 54. Then immediately drop in each eye one or two drops of a 1 per cent solution of nitrate of silver, and continue its use so long as it may be necessary.

SEC. 55. Half an hour after each application of the silver solution, wash the eyes with warm salt and water (a teaspoonful of table salt to a pint of boiled water) or with a solution of boric acid (10 grains to 2 tablespoonfuls of boiled water) and continue this last application every hour or two until the eyes are well, gradually lengthening the time.

SEC. 56. This disease is very contagious, even to grown persons, therefore burn or boil all cloths that have touched the eyes, avoid kissing the child, wash the hands after bathing the child's eyes, and allow no one else to use the same basin in which the child is bathed.

SEC. 57. Any person guilty of violation of any of the provisions of this order shall, upon conviction thereof, be punished by a fine of not less than ten dollars (\$10) nor more than two hundred dollars (\$200), or imprisonment for not less than ten (10) nor more than ninety (90) days, or by both such fine and imprisonment, at the discretion of the court.

RHODE ISLAND.

(General laws of 1909. Chapter 343.)

SEC. 25. Should any midwife or nurse, or person acting as nurse, having charge of an infant in this State, notice that one or both eyes of such infant are inflamed or reddened at any time within two weeks after its birth, it shall be the duty of such midwife or nurse, or person acting as nurse, so having charge of such infant, to report the fact in writing within six hours to the health officer or some qualified practitioner of medicine, of the city or town in which the parents of the infant reside.

SEC. 26. Every health officer shall furnish a copy of sections 25, 26, and 27, of this chapter to each person who is known to him to act as midwife or nurse in the city or town for which such health officer is appointed, and the secretary of state shall cause a sufficient number of copies of said sections to be printed, and supply the same to such health officers on application.

SEC. 27. Every person who shall fail to comply with the provisions of the two sections next preceding shall be fined not exceeding one hundred dollars, or imprisoned not exceeding six months, or both.

¹ Given force of law by sec. 8, p. 79, 31 Stats. L.

SOUTH CAROLINA.

(Criminal Code, 1902.)

SEC. 331. Should one or both eyes of an infant become reddened or inflamed at any time after birth, it shall be the duty of the midwife or nurse or person having charge of said infant to report the condition of the eyes at once to the local board of health of the city or town in which the parents of the infant reside.

Any failure to comply with the provisions of this section shall be punishable by a fine not to exceed twenty-five dollars, or imprisonment not to exceed one month, or both.

This section shall not apply to towns or cities of less than one thousand inhabitants.

TENNESSEE.

(Ch. 10, acts of 1911.)

SEC. 1. A person who, being a midwife, nurse, or other person having the care of an infant within the age of two weeks, neglects or omits to report immediately to the health officers or to a legally qualified practitioner of medicine of the city, town, or place where such child is being cared for, the fact that one or both eyes of such infant are inflamed or reddened whenever such shall be the case, or who applies any remedy therefor without the advice or except by the directions of such officer or physician, or neglects, refuses, or omits to comply with the above requirements shall be guilty of a misdemeanor.

TEXAS.

(Acts of 1909, ch. 30.)

SEC. 10 (as amended by ch. 95, acts of 1911). * * * Rule 22. Whenever any nurse, midwife, or other person not a legally qualified practitioner of medicine shall notice inflammation of the eyes or redness of the lids in a new-born child under his or her care, it shall be the duty of such person to report the same to the local health authority, or in his absence any reputable physician, within twelve hours of the time the disease is first noticed. * * *

Any person who shall violate any of the rules, regulations, or provisions of the sanitary code of Texas, as herein set forth, shall be deemed guilty of a misdemeanor and upon conviction shall be fined in any sum not less than ten dollars and not more than one hundred dollars.

UTAH.

(Acts of 1911, ch. 61.)

SEC. 1. It shall be the duty of every physician and every midwife attending a case of childbirth to report to the local board of health every case where the newly born child has inflammation of the eyes attended by a discharge therefrom. Such report to be made within six hours after the appearance of such disease. It shall be the duty of such physician or midwife to treat the eyes of the child so afflicted in accordance with the rules of the State board of health. Every physician and midwife failing to comply with the provisions of this act shall be guilty of a misdemeanor.

(Rules, State board of health.)

Rule 1. No midwife shall treat any case of ophthalmia neonatorum or inflammation of the eyes of a newly born infant unless it is impossible to secure the services of a physician, provided that in case the services of a physician shall be secured, a midwife may begin and carry out treatment until his arrival.

Rule. 2. In the event that the services of a physician can not be secured, midwives are authorized to use and apply the following treatment:

Immediately upon the discovery in a newly born infant of an inflammation of the eyes, attended by a mattery discharge therefrom, 5 drops of a 20 per cent solution of argyrol shall be dropped into the eyes with an eye dropper, after having separated the lids with the thumb and finger; and this treatment shall be repeated every hour for four days, and longer if a discharge is still present. After four days, if the discharge has ceased, the treatment may be reduced in frequency to intervals of four times daily for several days, until it is shown that the discharge is not liable to return.

Before each application of the argyrol solution, the eyes should be thoroughly irrigated, and cleansed by dropping or pouring into them a 1 per cent solution of chloride of sodium (common salt) or a saturated solution of boric acid. For practical purposes, the salt solution may be prepared by dissolving one teaspoonful of salt in a pint of water.

NOTE.—The person treating the eyes should exercise the utmost care to avoid touching the cornea (eyeball), as there is great danger of causing serious injury thereby. In applying the treatment the child should be placed flat upon its back and the head so held that the solution will not quickly escape from the eyes.

Inasmuch as the secretions from the eyes are very infectious, care should be taken to destroy all articles contaminated by them, and to sterilize the hands after each treatment.

The treatment above described is considered by eminent authorities to be entirely effective and safer than solutions of nitrate of silver; and it is recommended to all physicians in general practice.

Solutions of argyrol quickly deteriorate and should be freshly prepared for every case. Upon request the State board of health will furnish materials for preparing fresh solutions.

It is recommended that physicians and midwives shall make one application of the argyrol solution at the birth of every child as a prophylactic or preventive treatment, after having first thoroughly wiped the eyes with absorbent cotton or soft clean linen and bathed them with a saturated solution of boric acid.

Rule 3. On receipt of notification under this act, it shall be the duty of the local health officer to immediately investigate the case and satisfy himself that the rules of the State board of health are properly complied with. He shall also immediately report the case to the State board of health by telephone or telegraph.

VERMONT.

(Ch. 220, acts of 1910.)

SEC. 1. The State board of health are hereby empowered to make such rules and regulations as they may deem necessary for the prevention of blindness caused by the disease known as ophthalmia neonatorum, and they may furnish at public expense such prophylactic outfits as are necessary for the use of physicians.

SEC. 2. Any physician who fails to comply with the regulations established under section 1 of this act shall be fined ten dollars for each offense, and it shall be the duty of the State's attorney to prosecute in all cases on complaint of a local board of health.

WISCONSIN.

(Annotated Statutes, 1898.)

SEC. 1409a (added by ch. 59, acts of 1909). 1. The State board of health and vital statistics is vested with power and authority to publish and distribute among the physicians, midwives, nurses, or other persons requiring such information, instructions relating to inflammation of the eyes of newborn babes and proper methods of prevention. The board is hereby empowered to make and enforce such rules and regulations as it may deem expedient to prevent the development of inflammation of the eyes of the newborn babe, or so-called ophthalmia neonatorum.

SEC. 1409a-2. 1. It shall be the duty of the attending physician, midwife, nurse, or other person in attendance on a confinement case to use such prophylactic treatment for the prevention of blindness among newborn children as the State board of health and vital statistics in its rules and regulations may determine are necessary. Should one or both eyes of an infant become inflamed, swollen and red, and show an unnatural discharge at any time within two weeks after its birth, the nurse, parents, or other attendant having charge of such infant shall report in writing, within six hours thereafter, to the board of health of the city, incorporated village, or town in which the parents of the infant reside, the fact that such inflammation, swelling, redness, or unnatural discharge exists.

2. On receipt of such report the health officer shall inform the attending physician of the conditions complained of, or if there is no physician in attendance the health officer shall then employ at the expense of the town, incorporated village, or city, a competent physician to examine the case reported and the physician shall provide proper treatment or such as recommended in the rules and regulations adopted by the State board of health and vital statistics.

3. The health officer shall immediately upon the receipt of the written report herein provided for, if no physician was in charge, notify the parents or person having charge of said infant of the dangers to the eye or eyes of said infant, and he shall also inclose to the parents or person having charge of the child directions for the proper treatment thereof.

SEC. 1409a-3. Any woman accustomed to attend confinement cases shall be subject to the same penalty for violation as physicians or nurses.

SEC. 1409a-4. Any person who violates, neglects, or refuses to observe the provisions of this act shall be punished by a fine of not more than one hundred dollars for each offense.

DECISIONS.

One who, with no natural or legal duty, voluntarily seeks and assumes the care and instruction of a child is amenable to the statute if he fails to perform the duty required, to the injury of the child. (*Cowley v. People*, 83 N. Y., 464.)

A statute making a person liable for willfully omitting to perform the duty imposed upon him by law to furnish medical attendance to a minor places the duty of furnishing such attendance upon the one upon whom the law imposes the obligation of caring for the minor.

The constitutional guaranty of religious freedom is not violated by a statute requiring the furnishing of medical attendance to minors where the Constitution provides that liberty of conscience shall not justify practices inconsistent with the safety of the State. (*People v. Pierson*, 176 N. Y., 201.)

LIST OF PUBLIC HEALTH BULLETINS.

The following is a list of the Public Health Bulletins that have been issued:

- *1. Report on Trichinæ and Trichinosis. By W. C. W. Glazier. 1881. 212 pages. 87 il. 1 map. Paper. Senate Executive Document No. 9, Forty-sixth Congress, third session. Out of print.
- *2. Report on the Etiology and Prevention of Yellow Fever. By George M. Sternberg. 1890. 271 pages. 21 pl. 20 il. Cloth. Out of print.
- *3. Mortality Statistics in the United States for the year ending December 31, 1897. From Annual Report Marine-Hospital Service, 1898. 24 pages. Paper. Out of print.
4. Yellow Fever: Its Nature, Diagnosis, Treatment, and Prophylaxis and Quarantine Regulations Relating thereto. By officers of the Marine-Hospital Service. Reprint from Annual Report Marine-Hospital Service, 1898. 176 pages. 1 il. Paper.
- *5. Shipment of Merchandise from a Town infected with Yellow Fever. By H. R. Carter. 1899. 15 pages. Paper. Out of print.
6. Report of Commission of Medical Officers detailed by authority of the President to Investigate the Cause of Yellow Fever. By Eugene Wasdin and H. D. Geddings. July, 1899. 98 pages. 26 charts. 2 il. Paper.
- *7. The Bubonic Plague. By Walter Wyman. January, 1900. 50 pages. Paper. Superintendent of Documents, 5 cents.
- *8. Report of Commission appointed by the Secretary of the Treasury for the Investigation of Plague in San Francisco. By Prof. Simon Flexner, Prof. F. G. Novy, and Prof. L. F. Barker. January 23, 1901. 23 pages. 1 map. Paper. Out of print.
- *9. Report Relating to the Origin and Prevalence of Leprosy in the United States. By a Commission of Medical Officers of the U. S. Marine-Hospital Service. 1902. 119 pages. 25 il. Paper. Senate Document No. 269, Fifty-seventh Congress, first session. Superintendent of Documents. Cloth, \$1.00.
- *10. Plague Conference. Containing a copy of the address of the chairman, and resolutions passed by a conference called in accordance with requests from a number of State Boards of Health, and under authority of section 7, act of Congress approved July 1, 1902, to consider the plague situation. Reprint from P. H. R. No. 4, Vol. XVIII, January 23, 1903. 9 pages. And February 6, 1903. 41 pages. Paper. Out of print.
- *11. Transactions of the First Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. June, 1903. 120 pages. Cloth. Out of Print.
12. Transactions of the Second Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. June, 1904. 95 pages. Cloth.
13. The Public Health and Marine-Hospital Service of the United States. A Brief History. Prepared for the Louisiana Purchase Exposition. December, 1904. 16 pages. Paper.
- *14. Sanatorium for Consumptives, Fort Stanton, N. Mex. By P. M. Carrington. Reprint from Annual Report Public Health and Marine-Hospital Service, 1904. 19 pages. Paper. Out of print.

* Exhausted and not for distribution.

15. Transactions of the Third Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. May, 1905. 52 pages. Cloth.
16. How to Prevent Yellow Fever—No Mosquitoes, No Yellow Fever. By Walter Wyman. July 31, 1905. 3 pages. Circular.
17. Transactions of the Fourth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. May, 1906. 75 pages. Cloth.
18. Transactions of the Fifth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. May, 1907. 47 pages. Cloth.
19. Trachoma, Its Character and Effects. By Taliaferro Clark, and J. W. Scherschewsky. 1907. 34 pages. 6 il. Paper.
- *20. The Public Health and Marine-Hospital Service of the United States. A Brief History. Prepared for the Jamestown Ter-Centennial Exposition. 1907. 12 pages. Paper. Out of print.
- *21. Transactions of the Sixth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. April, 1908. 79 pages. Cloth. Out of print.
- *22. The Present Pandemic of Plague. By J. M. Eager. 1908. 30 pages. Paper. Out of print.
- *23. Pellagra—A Precis. By C. H. Lavinder. July 24, 1908. 22 pages. 1 il. Paper.
24. The Marine-Hospital Sanatorium, Fort Stanton, N. Mex. Prepared for the International Congress on Tuberculosis, held in Washington, September, 1908. 32 il. 56 pages. Paper.
- *25. Hookworm Disease. Reprint from Annual Report, P. H. and M. H. S., 1908. 5 pages. Paper. Out of print.
26. Studies upon Leprosy.
 - I. The Present Status of the Leprosy Problem in Hawaii.
 - II. The Reaction of Lepers to Moro's "Peicutaneous" Test.
 - III. A Note Upon the Possibility of the Mosquito Acting in the Transmission of Leprosy. By W. R. Brinckerhoff. 1908. Investigations made in accordance with the act of Congress approved March 3, 1905. 24 pages. Paper.
27. Studies upon Leprosy.
 - IV. Upon the Utility of the Examination of the Nose and the Nasal Secretions for the Detection of Incipient Cases of Leprosy. By W. R. Brinckerhoff and W. L. Moore. 1909. Investigations made in accordance with the act of Congress approved March 3, 1905. 29 pages. Paper.
28. Studies upon Leprosy.
 - V. A Report upon the Treatment of Six Cases of Leprosy with Nastine (Deyeke). By W. R. Brinckerhoff and J. T. Wayson, Honolulu, T. H.
 - VI. Leprosy in the United States of America in 1909. By W. R. Brinckerhoff. 1909. Investigations made in accordance with the act of Congress approved March 3, 1905. 25 pages. Paper.
- *29. The Prevalence of Rabies in the United States. By J. W. Kerr and A. M. Stimson. 1909. 16 pages. Paper. Out of print.
- *30. The Rat and its Relation to the Public Health. By various authors. 1910. 254 pages. 60 figs. 6 pls. Paper. Exhausted.
 1. Introduction. By Walter Wyman.
 2. Natural History of the Rat. By D. E. Lantz.
 3. Plague Infection in Rats. By G. W. McCoy.

- *30. The Rat and its Relation to the Public Health—Continued.
4. Rat Leprosy. By W. R. Brinckerhoff.
 5. Bacterial Diseases of the Rat other than Plague. By D. H. Currie.
 6. Organic Diseases of the Rat. By G. W. McCoy.
 7. Ecto Parasites of the Rat. By N. Banks.
 8. Intestinal Parasites of Rats and Mice in their Relation to Diseases of Man.
By C. W. Stiles.
 9. Rodents in Relation to the Transmission of Bubonic Plague. By Rupert Blue.
 10. Rodent Extermination. Rats and Mice. By W. C. Rucker.
 11. Natural Enemies of Rats. By D. E. Lantz.
 12. Rat-Proofing as an Anti plague Measure. By R. H. Creel.
 13. Inefficiency of Bacterial Viruses in the Extermination of Rats. By M. J. Rosenau.
 14. Plague Eradication in Cities by Sectional Extermination of Rats and General Rat-Proofing. By Victor G. Heiser.
 15. The Rat in Relation to Shipping. By W. C. Hobdy.
 16. The Rat as an Economic Factor. By D. E. Lantz.
 17. The Rat in Relation to International Sanitation. By J. W. Kerr.
- *31. Transactions of the Seventh Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. June, 1909. 86 pages. Cloth. Exhausted.
32. Hookworm Disease (or Ground-Itch Anemia), its Nature, Treatment, and Prevention. By Prof. C. W. Stiles. 1910. 40 pages. Paper.
 33. Studies upon Leprosy. 1910. 25 pages. Paper.
 - VII. A Statistical Study of an Endemic Focus of Leprosy. By W. R. Brinckerhoff and A. C. Reinecke.
 - VIII. A Palliative Treatment for Leprous Rhinitis. By J. T. Wayson and A. C. Reinecke.
 34. Maritime Quarantine. By L. E. Cofer. 1910. 25 figs. 64 pages. Paper. Appendix: Disinfectants Authorized by United States Quarantine Regulations and the Proper Method of Generating and Using Same.
 35. The Relation of Climate to the Treatment of Pulmonary Tuberculosis. By F. C. Smith. 1910. 17 pages. Paper.
 36. Tuberculosis: Its Nature and Prevention. By F. C. Smith. 1910. 12 pages. 1 plate. Paper.
 37. The Sanitary Privy: Its Purpose and Construction. By Prof. C. W. Stiles. 1910. 24 pages. 12 figs. Paper.
 38. General Observations on the Bionomics of the Rodent and Human Fleas. By M. B. Mitzmain. 1910. 34 pages. Paper.
 39. Studies upon Leprosy. September, 1910. 50 pages. Paper.
 - IX. Mosquitoes in Relation to the Transmission of Leprosy.
 - X. Flies in Relation to the Transmission of Leprosy. By D. H. Currie.
 - XI. Heredity Versus Environment in Leprosy. By H. T. Hollmann.
- *40. Transactions of the Eighth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. November, 1910. 101 pages. Paper. Exhausted.
41. Studies upon Leprosy. November, 1910. 36 pages. Paper.
 - XII. Notes on the Study of Histories of Lepers from the Standpoint of Transmission. By D. H. Currie.
 - XIII. A Contribution to the Study of Rat Leprosy. By D. H. Currie and H. T. Hollmann.

IV

42. Disinfectants: Their Use and Application in the Prevention of Communicable Diseases. By T. B. McClintic. December, 1910. 46 pages. Paper.
43. Experimental Studies of Plague and a Plague-like Disease among Rodents. By George W. McCoy. April, 1911. 71 pages. 7 pls. Paper.
44. Acute Anterior Poliomyelitis (Infantile Paralysis). By Wade H. Frost. February, 1911. 52 pages. Paper.
45. A Digest of the Laws and Regulations of the Various States Relative to the Reporting of Cases of Sickness. By J. W. Trask.
46. Transactions of the Ninth Annual Conference of State and Territorial Health Officers with the United States Public Health and Marine-Hospital Service. September, 1911.
47. Studies upon Leprosy. By D. H. Currie, Moses T. Clegg, and H. T. Hollmann. September, 1911.
 - XIV. The Artificial Cultivation of the Bacillus of Leprosy.
 - XV. Attempts at Specific Therapy in Leprosy.
48. Pellagra: A Précis. (Revised edition.) By C. H. Lavinder. September, 1911.
49. Ophthalmia Neonatorum. An Analysis of the Laws and Regulations Relating Thereto in Force in the United States. By J. W. Kerr. October, 1911.

O

PUBLIC HEALTH BULLETIN No. 50

OCTOBER, 1911

STUDIES UPON LEPROSY

XVI. IMMUNITY

BY

DONALD H. CURRIE
PASSED ASSISTANT SURGEON, DIRECTOR

AND

MOSES T. CLEGG
ASSISTANT DIRECTOR, LEPROSY INVESTIGATION STATION

XVII. FURTHER OBSERVATIONS IN RAT LEPROSY

BY

DONALD H. CURRIE
PASSED ASSISTANT SURGEON, DIRECTOR

AND

HARRY T. HOLLMANN
ACTING ASSISTANT SURGEON, LEPROSY INVESTIGATION STATION

XVIII. A STATISTICAL STUDY OF THE NASAL LESIONS IN LEPROSY

BY

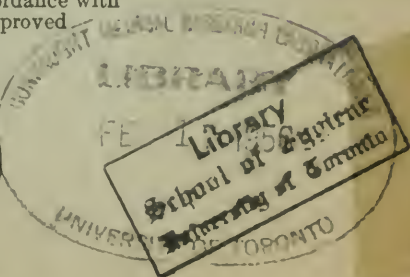
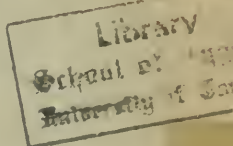
HARRY T. HOLLMANN
ACTING ASSISTANT SURGEON, LEPROSY INVESTIGATION STATION

Investigations made in accordance with
the Act of Congress approved
March 3, 1905



WASHINGTON
GOVERNMENT PRINTING OFFICE

1912





TREASURY DEPARTMENT
Public Health and Marine-Hospital Service of the United States

PUBLIC HEALTH BULLETIN No. 50-57

OCTOBER, 1911

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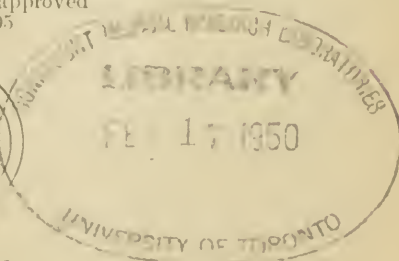
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IMMUNITY.

By DONALD H. CURRIE, *Passed Assistant Surgeon, Director,*
and
MOSES T. CLEGG, *Assistant Director, Leprosy Investigation Station.*

Since Bordet and Gengou (1) published their work on the complement fixation as one method of identifying *Bacillus typhosus*, it was hoped that this means of differentiating microorganisms would be specific, especially for those which would produce antibodies when inoculated into suitable animals. It has been found, however, that only certain bacteria contained the properties of binding the alexine or complement with their specific antibodies and then only when suitable extracts were prepared. It has also been shown that very small amounts of extracts of certain microorganisms will absorb the complement. We found this particularly true with the extracts of various acid fast bacilli, such as *Margarin bacillus*, *Smegma bacillus*, Möller's *Grass bacillus*, and *B. lepræ*.

The preparation of the extracts with special regard to the biochemistry of the microorganisms is essential and the method of their preparation should be given in detail.

Since the cultivation of the leprosy bacillus we have attempted by means of complement deflection to prove the acid fast bacillus cultivated by us was *B. lepræ*. It has been shown that the blood serum of lepers contained antibodies when combined with a suitable antigen, fixed the complement, and that, further, the antigenic substances used were closely allied to those producing the well-known Wassermann reaction.

Wechselmann and Meier (2) state they were able to fix the complement by using syphilitic antigen and serum from leprosy patients.

Eitner, Ernst, (3) used watery extracts of lepers' tissue as antigen. He states, however, that alcoholic extracts of guinea pigs' heart muscle produced the same positive results.

Bauer, Richard, and George Meier (4) state they found in the blood serum of 28 cases of leprosy antibodies which would fix complements with tuberculin and syphilitic antigen. They also state

that syphilitics (nonlepers), while giving a positive Wassermann reaction, did not fix the complement when tuberculin was used as the antigen.

Yundell, Almquist, and Sandman (5) were able to get a positive Wassermann reaction in 4 cases and a partial reaction in 4 cases of 24 lepers examined.

Slatineanu, A. and Danielopolu (6), however, claim that lepers' sera binding with tuberculin is convincing evidence that the patients are suffering with tuberculosis.

Slatineanu, A. and Danielopolu (7) found in the blood serum of 95 per cent of cases tested for Wassermann reaction antibodies fixing complement. They state that the degree of reaction varied in limited proportions.

Frugoni, Cesare (8), tested the sera from four nonsyphilitic lepers and was able to get a positive reaction in two cases.

Ehlers and Bourret (9) used the alcoholic extract of normal guinea pig's heart as antigen. They noted antibodies in the serum of lepers, and the degree of reaction varied from time to time in the same patient. They conclude the degree of reaction is no index to the severity of the disease.

Eliasberg, J. (10), states that leper's serum fixes complement in the presence of syphilitic antigen in 80 per cent of the number of cases he examined.

Frugoni, Cesare, and Pirani, S. (11), used the following as antigens, combined with leper's serum: Syphilitic, leproma, sarcoma, carcinoma, tuberculin and Koch's bacilli emulsion. Of the antigens used, they state that syphilitic antigen and tuberculin fixed the complement in a large percentage of cases, while the extract of lepromata fixed the complement in only a small percentage.

Bruck and Gessner (12) tested the blood serum of 10 lepers for the Wassermann reaction, 5 of which they claim gave positive results.

Kleinschmidt (13) claims to have produced complement binding antibodies in lepers by the subcutaneous injection of "Nastin," and that "Tuberculo-Nastin" will bind the complement with the serum of certain tubercular patients. This reaction he thinks may be due to the presence of the lipoids. Kleinschmidt also states that when lepers were injected with Chaulmoogra oil, complement binding antibodies were found in the serum, and that specific reaction exists, according to his experiments with the antibodies against the fats, "Nastin" and Chaulmoogra oil.

Serra (14) used the following antigens: Syphilitic liver extract, extract of leper nodules, extract of nonulcerating syphilitic nodes, lecithin and extracts of normal organs. In his conclusions he emphasizes what he considers to be the fact, that the serum of lepers possesses a greater affinity to the leprosy nodule extract than to the other

antigens. This, in his opinion, speaks for a relative specificity of the Wassermann reaction in leprosy.

Fox (15) using the syphilitic antigen, tested the serum of 38 cases of nodular leprosy for Wassermann reaction. Of this number, 31 gave positive results. None of the patients gave a history of lues.

In reviewing the above literature there is little doubt as to the presence of antibodies in the serum of patients suffering with leprosy; and these antibodies may be analogous to the antibodies in luecic patients, which latter bind the complement when certain lipoids are used as antigens.

Working with several of the acid fast bacilli, the fatty substances of the microorganisms were found to be anticomplementary when a relative small amount was used; and where true complement deflection occurred this phenomenon not only applied to extracts of the lepra bacillus, but to extracts of certain other bacilli belonging to the acid fast group.

Extracts of the following microorganisms were made and tested for their anticomplementary properties, and for their complement binding substances with serum from patients suffering with various types of leprosy, as well as with serum from animals, which had received several injections of the cultivated leprosy bacilli.

Lepra Bacillus "G."—This microorganism was cultivated from a nodule of an advanced case of tubercular leprosy, and had been growing on artificial media two years.

Lepra Bacillus "F."—Cultivated from the spleen of an advanced case of leprosy. This microorganism had been growing on artificial media two years.

Lepra Bacillus "B."—Cultivated from a nodule in the ear of a leprous patient and growing on artificial media one year.

Lepra Bacillus "H."—Cultivated from a nodule of a leprous patient and growing on artificial media three months.

Margarin Bacillus.—A nonpathogenic acid fast microorganism.¹

Smegma Bacillus.—A nonpathogenic acid fast microorganism.

Grass Bacillus Möller.—A nonpathogenic acid fast microorganism.

Urine Bacillus.—A nonpathogenic acid fast microorganism.

Butter Bacillus.—A nonpathogenic acid fast microorganism.

PREPARATION OF EXTRACTS.

Extract A.—Acetone insoluble product. A quantity of a 10-day-old culture was dissolved in equal parts of chloroform, alcohol, and ether, and placed in a water bath at near 70° centigrade until all the ether and most of the chloroform had evaporated. The flask was then set aside for one hour, and afterwards filtered through porce-

¹The nonpathogenic acid fast microorganisms used in these experiments were received from the Harvard Medical School.

lain; the filtrate was then evaporated to dryness, in vacuo, at a low temperature. A bright orange-yellow substance was deposited at the bottom of the flask. This deposit was covered with acetone, and the above-mentioned substance allowed to extract for two hours; the acetone (which had become yellow) was then decanted off. The acetone insoluble residue was dried to remove all traces of the acetone. A mixture of equal parts of alcohol, chloroform, and ether was added to the residue, which caused the latter to readily dissolve.

Extract B.—Bodies of the bacilli, which had been previously extracted with alcohol, chloroform, and ether, were dried and ground in agate mortar without the addition of glass or other foreign material, after the method of Koch in his preparation of "Bacillary Emulsion." The dried extracted bodies of the bacilli were taken up with a few cubic centimeters of normal salt solution and allowed to extract 24 hours.

Extract C.—From 20 agar slant cultures, which had been growing for one month, the microorganisms were removed and placed in 100 cubic centimeters of a mixture of equal parts of chloroform and ether, and kept at a temperature of 37° centigrade for 48 hours. The bacilli at first floated and then later settled to the bottom of the fluid. The alcohol and chloroform was separated from the bacilli by filtering through porcelain. The residue was then further extracted for a short time with ether and again filtered. The alcohol-chloroform and the ether extracts were mixed, and to the mixture was added 10 cubic centimeters each of distilled water and glycerin. The alcohol-chloroform and ether were removed by a current of unheated air, reducing the bulk to 20 cubic centimeters.

Extract D.—Ten-day-old cultures were partially dissolved in alkalized hydrogen peroxide and a substance precipitated from solution with 60 per cent alcohol. The precipitate, a white flocculent substance, was collected and washed with the following: Cold absolute alcohol, hot absolute alcohol, alcohol and ether, alcohol and chloroform, and lastly chloroform. The chloroform was evaporated and the precipitate was dissolved in glycerin. Before using, an equal part of water was added.

Extract E.—Ten-day-old cultures were ground in normal salt solution with glass, and allowed to extract 48 hours.

The titer of each of the above extracts was made, and the amount used was one-half of the maximum amount that would not absorb the complement necessary to completely hemolyse a 5 per cent suspension of sensitized erythrocytes.

In titering the various extracts, it was found that several, notably extracts A and B, absorbed the complement in exceedingly small amounts, and the point below this amount failed to bind the complement when brought in contact with their specific antibodies.

Of the above extracts only those substances extracted by the methods D and E fixed the complement with the sera tested.

Glycerin extract of the acid fast bacilli and preparations made similar to Koch's old tuberculin failed to bind the complement with lepers' serum or with the serum of animals which had received several injections of the acid fast bacilli.

TABLE NO. I.

Serum.	Amount of extract.	Bacillus Lepra II.	Bacillus Lepra B.	Bacillus Lepra F.	Bacillus Margarin.	Bacillus Smegma.
Extract "D":						
Monkey—	c. c.					
No. 82.....	0.05	Hemolysis	Hemolysis	Hemolysis	Hemolysis	Hemolysis.
No. 84.....	.05					
No. 8.....	.05					
Leper patient—						
No. 28.....	.05	Blocking..	Blocking..	Blocking..	Blocking..	
No. 29.....	.05					
No. 30.....	.05					
No. 8.....	.05	Blocking..	do.....	do.....	do.....	
Horse, No. 44.....	.05	Partial..	Partial..	do.....	Partial..	Partial.
Normal.....	(1)	Hemolysis	Hemolysis	Hemolysis	Hemolysis	Hemolysis.
Extract "E":						
Leper patient—						
No. 28.....	.1	Partial....	Partial....	Partial....	Partial....	Do.
No. 29.....	.1	do.....	Hemolysis	do.....	do.....	Do.
No. 30.....	.1	do.....	do.....	do.....	do.....	Do.
No. 8.....	.1	Blocking..	Partial....	do.....	Blocking..	Do.
Monkey—						
No. 82.....	.1	Hemolysis	Hemolysis	Hemolysis	Hemolysis	Do.
No. 84.....	.1					
No. 8.....	.1					
Horse, No. 44.....	.1	Partial....	Partial....	Partial....	Partial....	Do.
Normal.....	.1	Hemolysis	Hemolysis	Hemolysis	Hemolysis	Do.
Extract "A":						
Leper patient—						
No. 28.....	.02	do.....	do.....	do.....	do.....	Do.
No. 29.....	.02					
No. 30.....	.02					
Extract "C":						
Leper patient—						
No. 28.....	.02	do.....	do.....	do.....	do.....	Do.
No. 29.....	.02					
No. 30.....	.02					

1 Hemolysis.

Animals Nos. 82 and 84: Monkeys which had been previously injected several times with increasing amount of a suspension of leprosy bacillus "II."

Leper patients Nos. 28, 29, and 30: Advanced tubercular leprosy.

Leper patient No. 8: Very little evidence of leprosy at present. Patient has had the disease three years.

Animal No. 44: This horse had been injected several times with increasing amounts of a suspension of leprosy bacilli "II," "B," "F," and "G."

The hemolytic system used in the above experiments was inactivated antishoop rabbit serum, guinea-pig serum, as complement, and a 5 per cent suspension of sheep erythrocytes. Sets of control tubes were made as follows: Sera tested for their complement-absorbing properties and for their hemolytic properties to sheep erythrocytes. The same controls were made with the several extracts.

Our results showed no difference in the degree of complement deflection when using extracts of the leprosy bacillus than with a similar extract of the Margarin bacillus. That certain extracts of the artificially grown leprosy bacilli and extracts made from lepra nodules will deflect complement when combined with lepra serum is evident.

Eitner (16) used as antigen a salt solution extract of leproma, and states he found in the serum of lepers antibodies which were capable of binding the complement.

Sugai (17), working with a similar extract, was able to procure the same results.

Babes and Busila (18) state they were able to fix the complement with lepers' sera when combined with an extract of a leproma which had been preserved in alcohol 10 years.

Steffenhagen, Karl (19), used as antigen the following extracts: Extract of leprosy nodules, extract of tubercle bacilli, old tuberculin, syphilitic antigen, extract of the typhoid bacilli, and extract of meningococcus. He prepared his leprosy-nodule extract by macerating the nodules or lymph glands of lepers and occasionally adding 10 per cent antiformin solution. The undissolved portion of the organ was separated by filtering. The solution was centrifuged and the sediment once more washed with antiformin solution and afterwards repeatedly washed with normal salt solution and again centrifuged. The sediment was dried and weighed to determine the amount of antigen. His extract of the sediment was prepared by rubbing and adding gradually drops of physiological salt solution. This experiment he claims showed that 1 milligram fixed the complement completely, without the addition of immune serum, and hemolysis only sets in when amounts of 0.6 milligram and less were employed. He therefore used in all of his experiments 0.5 milligram, and was able to deflect the complement when combined with leper serum in the majority of cases.

Babes and Busila (20) report that ethereal extract of bacillus of timothy hay will bind the complement in the presence of lepers' serum, but not with normal serum.

Since our work was begun Duval (21), in a recent article on the immunity of *B. lepræ*, states that he was able to deflect the complement by using the blood serum of lepers and a salt-solution extract of the lepra bacillus cultivated by him as antigen.

AGGLUTINATION.

In the following experiments we employed (a) serum from a horse which had received several injections of a suspension of live leprosy bacilli; (b) serum from lepra patients in various stages of the disease.

The horse was prepared by injecting intravenously, at intervals of 10 days, increasing amounts of the suspension of leprosy bacillus "H," as follows: The growth from four agar slant tubes—8 agar slant tubes and 16 agar slant tubes, respectively. These injections were followed by two subcutaneous inoculations of a suspension prepared from 10 agar slant cultures each of lepra bacilli "H." "G," "F," and "B."

Following the first two intravenous injections, the animal's temperature registered 40° centigrade and remained above 38° centigrade for five days. The subcutaneous inoculation produced an indurated area at the site of the inoculation, which went on to supuration; the contents of this abscess being later absorbed. One month after the last subcutaneous injection the animal was bled, and its serum was used for the complement deflection test (the results of which are given in the first part of this paper) and for the following agglutination experiments:

Suspensions of the growth of 10-day-old cultures of each strain of the acid-fast bacilli were made in small test tubes containing 5 cubic centimeters of normal salt solution. Approximately one loop of the culture was used to each tube. The different sera were added to the various suspensions in amounts sufficient to make the required dilutions. The experiment was controlled with similar suspensions without the addition of blood serum. All tubes were then placed at 37° centigrade, and the results read after a period of eight hours.

TABLE No. II.—Agglutination.

Serum.	Dilution.	<i>Lepra</i> bacillus "H."	<i>Lepra</i> bacillus "G."	<i>Lepra</i> bacillus "F."	<i>Lepra</i> bacillus "B."	<i>Lepra</i> bacillus "S."	Margarin bacillus.	<i>Synechia</i> bacillus.	Urine bacillus.	Grass bacillus.	Butter bacillus.
Horse, No. 41.....	1:100	+	+	—	—	—	0	0	0	0	0
	1:200	++	++	—	—	—	0	0	0	0	0
	1:500	+	+	—	—	—	0	0	0	0	0
	1:1,000	++	++	—	—	—	0	0	0	0	0
Leper patient, No. 8.....	1:50	+	+	—	—	—	0	0	0	0	0
	1:100	0	0	0	0	0	0	0	0	0	0
Leper patient, No. 29.....	1:50	0	0	0	0	0	0	0	0	0	0
Leper patient, No. 30.....	1:50	0	0	0	0	0	0	0	0	0	0

Duval (loc. cit.) was able to produce agglutinins in the serum of a horse by repeated injections of artificially grown leprosy bacillus. Clumping occurred, according to Duval, in dilution of 1 to 200.

CONCLUSIONS.

I. We were unable to differentiate by the method of Bordet and Gengou the leprosy bacillus from certain other acid-fast microorganisms.

II. Extracts of certain acid-fast bacilli, other than *B. lepra*, will deflect the complement when combined with lepers' serum.

III. We were able to produce specific agglutinins for *B. lepra* by injecting a horse with the cultivated lepra bacilli.

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FURTHER OBSERVATIONS IN RAT LEPROSY.

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In a previous bulletin¹ we recorded certain observations bearing on the pathology of rat leprosy, and from the data we had then secured we drew the following conclusions:

"1. In some cases of artificially acquired rat leprosy the onset is with broncho-pneumonia, accompanied by a septicemia and without other demonstrable lesions.

"2. In other cases of this disease pneumonia is a very early lesion, but we can not positively state that it is always the first lesion.

"3. That the animal may die in the pneumonic stage before other lesions present themselves, or it may develop pneumonic symptoms and recover from the same only to later develop the well-known lesions of chronic rat leprosy; or again, the pneumonia may persist until after the development of the lesions of the skin and abdominal viscera.

"4. That during the stage of the disease in which the animal is very ill, certain mites (*Laelaps echidninus*) were found to be very numerous on the animals' bodies.

"5. That during the stage of the disease in which septicemia is marked, these mites' digestive tracts contain the bacilli of rat leprosy in considerable numbers, and therefore these parasites may be one means of transmitting the disease. This latter probability, however, is, of course, not proven."

Upon the completion of the above-mentioned work, our infected animals having all succumbed to this disease, we inoculated 13 other white rats from the tissues of the animals that we had necropsied and found to be suffering from rat leprosy. We also set aside for observation 12 other rats that had been intimately exposed to this disease by living in the same cage with the animals suffering from rat leprosy.

¹ A Contribution to the Study of Rat Leprosy, by Passed Asst. Surg. Donald H. Currie, Director, and Harry T. Hollmann, Acting Asst. Surg., U. S. Leprosy Investigation Station, Honolulu, T. H., Public Health Bulletin No. 41, Public Health and Marine-Hospital Service of the United States, November, 1910.

The below-given data were secured from necropsying these apparently normal (so far as symptoms and appearance showed during the life of the animals) inoculated or exposed rats. Our findings therefore represent a very early stage of rat leprosy—so early as to not cause any appreciable symptoms. We therefore consider that these findings, coupled with the data we published in the previous bulletin, probably fairly represent the usual pathology of the early stage of this disease.

NECROPSY FINDINGS OF THE 13 RATS THAT WERE INOCULATED ON AUGUST 11, 1910, BY PLACING A SMALL PORTION OF THE TISSUE OF A RAT INFECTED WITH RAT LEPROSY UNDER THEIR SKINS.

Rat No. 1.—Chloroformed and necropsied on June 2, 1911. A hard nodule was found under the skin at the point of inoculation. This had become caseous and extended down to the underlying fascia. Small whitish nodules extended from this mass apparently along the lymphatics for the distance of about half an inch from the primary nodule. The near-by lymphatic gland was not enlarged. Smears from the primary nodule showed many acid-fast bacilli.

Spleen normal in size and appearance, but smears made from its cut surface showed numerous acid-fast bacilli.

Right lung: Emphysematous, except the lower part of the upper lobe, which was resistant to pressure and sank when thrown into water. This portion of the organ, cut with increased resistance, was entirely devoid of air, cut surface and pleura studded with white nodules. Purulent material exuded from its cut surface.

Left lung was completely consolidated; sank when thrown into water; pleura studded with white nodules; cut with increased resistance; cut surface exuded purulent material. Smears made from the purulent material of these organs, when stained in the usual manner, showed a few acid-fast bacilli, morphologically resembling the bacillus of rat leprosy.

We noted no lesions of skin or viscera other than those mentioned above.

Rat No. 2.—No local lesion found at point of inoculation. Layer of fatty material over abdomen, between abdominal muscles and skin, which material was rich in acid-fast bacilli. Both lungs were normal in appearance and contained no acid-fast bacilli.

Skin and viscera, other than above noted, were apparently normal.

Rat No. 3.—No alopecia or other lesions of skin except the healed wound at the point of inoculation. Incision was made through this cicatrix and revealed a small circumscribed cavity in the center, filled with pus of a cheesy nature. Examination of smears made from this material showed a large number of acid-fast bacilli.

Spleen slightly enlarged and smears made from it showed a considerable number of acid-fast bacilli per microscopical field.

Lungs: Both organs dark red in color, with small whitish nodules scattered throughout their substance. Portions of organs removed and found to sink when thrown into water. Both organs cut with resistance; cut surfaces exuded yellowish material. Smears made from this material showed a moderate number of acid-fast bacilli.

Rat No. 4.—Except for a slight scar at the point of inoculation, smears from which showed no acid-fast bacilli, the animal appeared to be entirely normal.

Rat No. 5.—A hard nodule, scar-like in character, situated at the site of inoculation. This was incised through and found to contain purulent material in its center. Smears made from this, when stained in the ordinary manner, showed many acid-fast bacilli.

With the exception of this, the skin and viscera of this animal appeared to be perfectly normal, and no acid-fast bacilli were found in smears from the other organs.

Rat No. 6.—Slight scar at the site of inoculation; a small ulcer of skin near by. A smear made from the secretions of this ulcer showed numerous acid-fast bacilli.

The spleen was normal in macroscopical appearance, but smears made from it showed acid-fast bacilli.

The inguinal and axillary glands were slightly enlarged; smears made from them, when stained in the ordinary manner, showed acid-fast bacilli.

Right lung: Upper lobe completely consolidated, dark red in color, with here and there yellowish nodules scattered throughout its substance. When cut, a small cavity was shown, containing cheesy material. Smear made from organ, stained in the ordinary manner, showed the presence of acid-fast bacilli.

Left lung presented a similar condition to that of its fellow.

The other viscera were normal in appearance.

Rat No. 7.—The site of inoculation showed a scarlike nodule, which was found to contain a pus-filled cavity in its center, which material was rich in acid-fast bacilli.

Spleen normal in appearance, no acid-fast bacilli could be demonstrated in the smears made from it.

Peribronchial glands greatly enlarged; yellowish brown in color and rich in acid-fast bacilli.

Lungs normal in appearance; smears made from them showed no acid-fast bacilli.

Rat No. 8.—A scarlike nodule at the site of inoculation, which, when incised through showed a cavity in the center containing a cheesylike material; this material was rich in acid-fast bacilli. The

lymphatic glands nearest this nodule were enlarged and showed acid-fast bacilli in smears made from them.

The lungs and other viscera were entirely normal in appearance and contained no acid-fast organisms.

Rat No. 9.—No pathological conditions met with in this animal, except a scarlike nodule at the site of inoculation, the center of which showed a cavity containing caseous material, rich in acid-fast bacilli.

Rat No. 10.—A small ulcer was found at the site of inoculation; the secretions from this ulcer contained acid-fast bacilli. The neighboring glands were not enlarged.

The spleen was studded with small, white nodules, and smears made from the organ showed many acid-fast bacilli present.

Lungs normal in appearance and showed no acid-fast bacilli present in smears made from them.

Rat No. 11.—No local lesions other than a slight scar at the site of inoculation. No ulceration, alopecia or other changes of the skin, no enlargement of the inguinal glands.

Spleen appeared to be normal, but smears made from it showed acid-fast bacilli to be present.

Right lung: Upper lobe consolidated, dark red in color, studded with yellowish nodules, cut with increased resistance, purulent material exuded from it. Smears made from this cheesy matter, stained in the ordinary manner, showed the presence of acid-fast bacilli.

Left lung: Much of the organ emphysematous, but one of the lobes showed a rather large yellowish nodule containing a cheesy material, which latter, when stained, showed the presence of acid-fast bacilli.

Heart blood showed a very few acid-fast bacilli.

Rat No. 12.—Skin normal, except for a scar at the site of inoculation.

Right lung: Upper and middle lobes of dark-red color, with yellowish nodules scattered throughout its substance. Organ sank when thrown into water. Yellowish creamy material exuded from cut surface, which material contained acid-fast bacilli. The lower lobe of the organ was normal.

The left lung was normal, except for what was apparently a compensatory emphysema.

Rat No. 13.—Animal appeared to be perfectly normal.

The following are the necropsy notes on 11 rats that were exposed to rat leprosy by placing them in a cage containing some well-advanced cases of that disease in animals of the same species. After being in contact for a period of several months these 11 animals were removed and placed by themselves. Nearly a year later the animals that had been exposed to the disease were necropsied, with the following results:

*Contact rat No. 1.*¹—Skin, subcutaneous tissue, and liver normal.

Lungs: Apices of both lungs dark red in color, consolidated, with yellowish nodules scattered throughout its substance; 10 such distinct nodules were noted in the two organs. Portion of the lungs when thrown into water, sank, and appeared to be entirely free from air. Smears made from it showed a few acid-fast bacilli. The remaining portion of the lungs was normal.

Contact rat No. 2.—Necropsy showed animal to be entirely normal.

Contact rat No. 3.—Poorly nourished animal. Abdomen contained a layer of fattylike material between skin and abdominal muscles, which material was rich in acid-fast bacilli.

Lungs: Upper lobe of right lung dark red in color, with yellowish nodules scattered through its substance. The consolidated portion of the organ sank when thrown into water. Left lung showed consolidation of one of its lobes; was of dark red color, containing yellowish nodules scattered through its substance. This portion of the organ sank when thrown into water. Smear made from the consolidated portion of the lungs and stained in the ordinary manner showed the presence of acid-fast bacilli.

The spleen was normal in appearance, but showed a few acid-fast bacilli in the smears made from it.

Contact rat No. 4.—Skin, glands, and viscera of this animal appeared to be normal, with the exception of the upper half of the upper lobe of the right lung, which was completely consolidated, and smear made from it and stained in the ordinary manner showed the presence of a few acid-fast bacilli.

Contact rat No. 5.—Body of animal appeared to be normal.

Contact rat No. 6.—Body of animal appeared to be normal.

Contact rat No. 7.—An area of alopecia on back, of irregular shape, 1 to 1½ centimeters in diameter. No fattylike deposits found in subcutaneous tissues. Liver and spleen were normal; inguinal glands appeared to be slightly enlarged, but no acid-fast bacilli were present in them.

Right lung: The greater portion of that organ was completely consolidated, of yellowish color, sank when thrown into water, cut with resistance. Cut surface exuded a cheesy material, containing acid-fast bacilli.

Left lung: Most of the organ was emphysematous, but its lower border presented a mass of closely placed yellowish nodules, which, when incised through, exuded a cheesy material. While this portion of the lung, in its gross anatomical appearance, resembled its fellow, no acid-fast bacilli could be demonstrated in this organ, but it was

¹To distinguish these animals from the first series we have placed the word "contact" before each of the numerals designating the various animals.

quite evident that the condition was the same as that affecting its fellow of the opposite side.

Contact rat No. 8.—Patch of alopecia on abdomen, two centimeters in diameter. A small, scar-like nodule over skin of abdomen, containing a cavity, filled with cheesy material, rich in acid-fast bacilli. (This lesion is interesting as the animal was never inoculated by us, hence the wound that caused the infected scar may have been the result of fighting amongst themselves.)

Spleen normal in appearance, contained no acid-fast bacilli.

Lungs showed small scattered areas of a deep red color throughout the organ, which areas, when dissected out and placed into water, sank, and otherwise showed all the signs of complete consolidation. Smears made from these consolidated areas showed acid-fast bacilli.

Smears made from heart blood showed a few acid-fast bacilli.

Two mites (*Laelaps echidninus*) were taken from this animal, smeared and stained, and each of these mites were found to contain acid-fast bacilli.

Contact rat No. 9.—Showed a slight thinning of the hair over the abdomen and the back, which may, however, have not been due to this disease, as the condition was not well marked. Otherwise the body of the animal appeared to be entirely normal.

Contact rat No. 10.—Large ulcer on abdomen, extending across entire left side, involving skin and subcutaneous tissue. This ulcer was 7 by 9 centimeters in extent.

Spleen studded with small white nodules, containing many acid-fast bacilli.

Liver enlarged, and smears made from its cut surface showed a few acid-fast bacilli.

Right lung: Whole organ markedly congested, some small areas probably consolidated. Smear made from the cut surface of organ showed acid-fast bacilli.

Left lung: The same as right lung, except in addition to these conditions there was a wedge-shaped area of a very dark color, evidently representing a red infarct. Cut surface of the organ showed acid-fast bacilli. The infarct was dissected out and incised separately, but smears made from its cut surface contained no acid-fast bacilli.

The heart blood showed a few acid-fast bacilli in the many fields examined.

The axillary glands were enlarged and contained a great number of acid-fast bacilli.

Contact rat No. 11.—There was an ulcer of the skin over the anterior aspect of the abdomen. This ulcer had made its way through the subcutaneous tissue and abdominal muscles to the peritoneum, but had not perforated the latter. Smears made from its discharges

showed a number of acid-fast bacilli. Peritoneum was deeply congested, but still retained its luster.

Spleen showed evidence of a perisplenitis and contained many acid-fast bacilli.

Liver studded with numerous small abscess cavities, scattered throughout the substance of the organ, the contents of which were rich in acid-fast bacilli.

Lungs: Upper lobes of both organs were consolidated, of a dark red color, showing no nodule formation. Smears made from cut surface showed large numbers of acid-fast bacilli.

Heart blood showed the presence of a considerable number of acid-fast bacilli.

There was an area of alopecia over the back of the animal.

Four mites (*Laelaps echidninus*) were removed from the animal's skin, smeared and stained in the usual manner, and all of them were found to contain acid-fast bacilli.

This rat evidently represented a more advanced stage of the disease than most of those that we have examined.

In the previous report referred to, under "Rat II," on page 20, we stated that 32, probably infected, mites were placed on 3 specimens of rats (*Mus alexandrinus*), and that 100 house flies were fed with the leprous subcutaneous tissue of a leprous rat and placed in a cage with two healthy rats (*Mus alexandrinus*), after the tails of these rodents had been abraded by scraping, so as to make them attractive to the flies, and also to afford a lesion for the possible entrance of the bacilli. We stated further, on the same page, that we would report at a later time on the results of these attempts to inoculate these animals by the use of the infected ecto-parasites or insects.

In this connection we can state, however, that after waiting for nearly one year, we chloroformed these five animals and necropsied them, but their bodies showed no evidence of infection with rat leprosy.

From the data secured in these animals, considered with the data given in our previous article on this subject, we are apparently justified in concluding that:

First. In the disease that we are dealing with, whether the animal is inoculated by a laboratory method or simply allowed to develop the disease from coming into contact with infected rats—i. e., the natural mode of infection—the lesions met with are practically the same.

Second. With the exception of the local lesion, occasionally produced at the site of artificial inoculation, infection of the viscera seems to usually precede the lesions of the skin.

Third. Of the visceral lesions, a broncho-pneumonia is often the earliest and the most constant. Infection of the spleen is also often an early event.

Fourth. The heart blood of infected rats often contains the bacilli of rat leprosy, and no difficulty is experienced in demonstrating the presence of acid-fast bacilli in the mites contained on the bodies of these animals, when the latter's heart blood contains the organisms.

Fifth. The fact that these mites contain the bacilli so frequently naturally leads one to suspect that they may be one of the means of transmitting the disease from rat to rat, but up to the present time we have no positive evidence that such is the case.

ATTEMPTS TO CULTIVATE THE BACILLUS OF RAT LEPROSY.

As reported in our first paper, we have made many attempts to cultivate the bacillus of rat leprosy on artificial culture media; both on the media ordinarily employed in the laboratory, and by the method of Clegg in symbiosis with amœba and cholera. We have now to report that we have continued these experiments for nearly a year, and that our results have been entirely negative, not having secured a single culture of an organism which we considered to be the bacillus of rat leprosy. In one of our attempts to cultivate this organism from the ulcer on the abdomen of a leprosy rat, we succeeded in growing what appeared to be an acid-fast streptothrix. As one might expect to obtain such organisms on an exposed surface of that kind, we regarded this culture as an accidental contamination, and not the bacillus of rat leprosy.

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A STATISTICAL STUDY OF THE NASAL LESIONS IN LEPROSY.

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INTRODUCTION.

The published work of Sticker, in 1897, increased the interest in the theory, mentioned in 1891 by Goldschmidt and (according to Glück, Wiener medizinische Wochenschrift, 1901) in 1896 by Kober, that the earliest lesions in leprosy were often found in the nasal mucosa.

The following table is based upon data secured by the examination of the nasal cavities of 500 persons suffering from leprosy. These 500 cases gave a history of having had the disease in a recognizable form for periods varying from 3 months to 25 years, and all of them showed unmistakable leprous lesions on other parts of the body at the time the examinations were made.

Results of the examination of the nasal mucous membrane of 500 lepers.

	Predominating gross lesions present.				Total examinations made.	
	Perforation of nasal septum.	Atrophic rhinitis.	Hypertrophic rhinitis.	Absorption of cartilage.	Lesions present.	Lesions absent.
Nodular type.....	27	15	13	97	152	19
Anæsthetic type.....	63	43	9	59	174	53
Mixed type.....	10	10	7	57	84	18
Total.....	100	68	29	213	410	90

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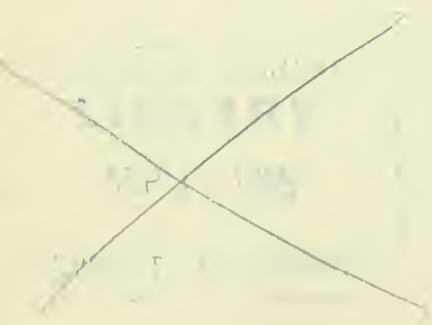
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